

**DESCRIPTION****NOVEL SULFONYL DERIVATIVES****Technical Field**

5           The present invention relates to a novel, orally-administrable sulfonyl derivative or salt thereof which inhibits an activated coagulation factor X (which will hereinafter be abbreviated as "FXa"), thereby exhibiting strong anticoagulant action; and a coagulation suppressor or preventive and/or remedy for thrombosis or embolism which comprises the derivative or salt as an effective ingredient.

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**Background Art**

Exasperation of coagulation activity is an important factor for unstable angina, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein thrombosis, disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization or formation of thrombus upon extracorporeal circulation. There is accordingly a demand for an excellent anticoagulant which is excellent in dose-responsiveness, has long-lasting effects, has a low risk of hemorrhage, has less side effects and exhibits rapid and sufficient effects even by oral administration (Thrombosis Research, 68, 507-512, 1992).

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Studies on anticoagulants based on various acting mechanisms suggest that a FXa inhibitor has a possibility of becoming an excellent anticoagulant. The coagulation system is a series of reactions wherein a large amount of a thrombus is produced through an amplification step due to a multi-stage enzymatic reaction and induces the formation of insoluble fibrin. In the intrinsic system, after the multi-stage reaction following the activation of a contact factor, activated Factor IX activates factor X on a phospholipid membrane in the presence of activated Factor VIII and a calcium ion, while in the extrinsic system, activated Factor VII activates Factor X in the presence of a tissue factor. In other words, the activation of Factor X into FXa in the coagulation system is an essential reaction in the formation of thrombin. Activated Factor X (FXa) in each system carries out limited proteolysis of prothrombin, thereby forming thrombin. The resulting thrombin activates the coagulation factors on the upstream side, whereby the formation of thrombin is amplified further. As described above, the coagulation system upstream of FXa is separated into intrinsic and extrinsic systems so that the inhibition of the enzyme of the coagulation system upstream of FXa does not suppress the production of FXa sufficiently, inevitably resulting in the production of thrombin. Furthermore, the coagulation occurs as a self-amplifying reaction so that the suppression of the coagulation system can be

accomplished more efficiently by the inhibition of FXa which exists upstream of the thrombin than by the inhibition of the thrombin formed (Thrombosis Research, **15**, 617-629(1979)).

5           Another merit of the FXa inhibitor is that an effective dose in a thrombus model is largely different from the dose for extending the bleeding time in an experimental hemorrhage model. From the experimental result, the FXa inhibitor is presumed to be an anticoagulant with a low  
10 risk of hemorrhage.

As a FXa inhibitor, various compounds are reported. In general, antithrombin III or antithrombin III-dependent penta-saccharide is known to have no inhibitory action against a prothrombinase complex which plays a practical  
15 role in the thrombus formation in vivo (Thrombosis Research, **68**, 507-512(1992); Journal of Clinical Investigation, **71**, 1383-1389(1983); Mebio, August issue, 92-97) and moreover, it does not exhibit effectiveness in oral administration. Although tick anticoagulant peptide (TAP) (Sci-  
20 ence, **248**, 593-596(1990)) or antistacin (AST) (Journal of Biological Chemistry, **263**, 10162-10167(1988)) isolated from a tick or leech which is a bloodsucker inhibits FXa and exhibits anti-thrombus effects on the models of from venous thrombus to arterial thrombus, it is not effective when  
25 orally administered because it is a high-molecular peptide. From such a viewpoint, a low-molecular FXa inhibitor which

directly inhibits a coagulation factor without depending on antithrombin III has been developed.

An object of the present invention is to provide, as an excellent anticoagulant, a novel sulfonyl derivative or salt thereof, or a solvate thereof which has strong FXa inhibitory action, exhibits prompt, sufficient and long-lasting anti-thrombus effects even by the oral administration and has less side effects.

#### 10      **Disclosure of the Invention**

With the forgoing in view, the present inventors have carried out an extensive investigation on the synthesis of a novel FXa inhibitor and its pharmacological action. As a result, it has been found that a novel sulfonyl derivative or salt thereof, or solvate thereof exhibits strong FXa inhibitory activity and strong anticoagulant activity, inhibits FXa strongly, promptly and continuously by the oral administration, exhibits anti-coagulant action and anti-thrombus action, is highly safe and is useful as a preventive or remedy for various diseases caused by a thrombus-embolus.

The present invention relates to a sulfonyl derivative represented by the below-described formula (I) or salt thereof, or a solvate thereof:

25      Chemical formula (I):





[wherein,  $Q^1$  represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent, a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent or a saturated or unsaturated tricyclic fused ring group which may have a substituent;

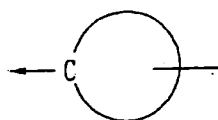
$Q^2$  represents a single bond, an oxygen atom, a sulfur atom, a linear or branched  $C_{1-6}$  alkylene group, a linear or branched  $C_{2-6}$  alkenylene group, a linear or branched  $C_{2-6}$  alkynylene group,

a group  $-N(R^1)-CO-$

(in which  $R^1$  represents a hydrogen atom or an alkyl group),

a group  $-N(R^2)-(CH_2)_m-$

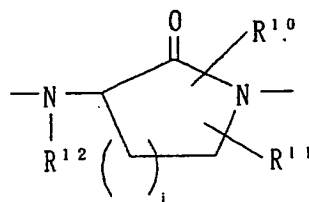
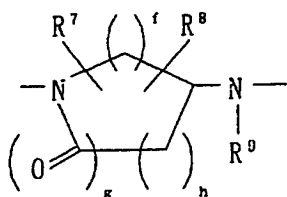
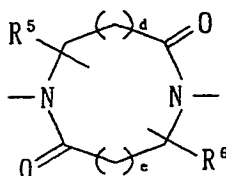
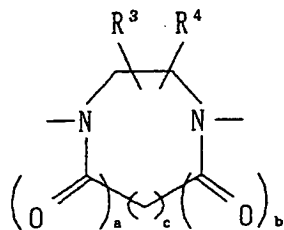
(in which  $R^2$  represents a hydrogen atom or an alkyl group and  $m$  stands for an integer of 0 to 6), or a group of the following formula:



(which represents a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent, a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent or a divalent, saturated or unsaturated dicyclic fused ring

group which may have a substituent and  $\leftarrow C$  means the bonding of the carbon atom of this group to  $Q^1$ ),

$Q^3$  represents any one of the following groups:



- 5 (in which when the carbon atom to which each of  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^{10}$  and  $R^{11}$  has been bonded is not adjacent to a nitrogen atom,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^{10}$  and  $R^{11}$  each independently represents a hydrogen atom,

a hydroxyl group,

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an alkyl group,

an alkoxy group,

an alkoxyalkyl group,

an alkoxyalkyloxy group,

a hydroxyalkyl group,

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a hydroxyalkyloxy group,

a hydroxyalkylcarbonyl group,

a hydroxyalkylsulfonyl group,

a formyl group,

- a formylalkyl group,
- a formylalkylcarbonyl group,
- a formylalkylsulfonyl group,
- an alkylcarbonyl group,
- 5 an alkylsulfonyl group,
- an alkylcarbonylalkyl group,
- an alkylsulfonylalkyl group,
- a carboxyl group,
- a carboxyalkyl group,
- 10 a carboxyalkyloxy group,
- a carboxyalkylcarbonyl group,
- a carboxyalkylsulfonyl group,
- a carboxyalkylcarbonylalkyl group,
- a carboxyalkylsulfonylalkyl group,
- 15 an alkoxycarbonyl group,
- an alkoxycarbonylalkyl group,
- an alkoxycarbonylalkyloxy group,
- an alkoxycarbonylalkylcarbonyl group,
- an alkoxycarbonylalkylsulfonyl group,
- 20 an amino group which may have one or two substituents,
- an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminoalkyloxy group which may have, at the amino moiety thereof, one or two substituents,
- 25 an aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents,

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, one or two substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents,

5 an aminocarbonylalkyl group which may have, at the amino moiety thereof, one or two substituents,

an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, one or two substituents,

10 an alkylsulfonylaminocarbonylalkyl group which may have, at the amino moiety thereof, one substituent,

an arylsulfonylaminocarbonyl group which may have, at the amino moiety thereof, one substituent,

an aminosulfonylalkyl group which may have, at the amino moiety thereof, one or two substituents,

15 a cyanoalkyl group,

an alkoxyalkylaminocarbonylalkyl group which may have, at the amino moiety thereof, one substituent,

an alkylcarbonyloxyalkyl group, or

20 a group  $A^1-B^1$ - (in which  $A^1$  represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and  $B^1$  represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group  $-O-(C_{1-6}$  alkylene), a group  $-COO-(C_{1-6}$  alkylene), a group  $-NHCO-$  or a  
25 group  $-NHCO-(C_{1-6}$  alkylene),

when the carbon atom to which each of  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^{10}$  and  $R^{11}$  has been bonded is adjacent to a nitrogen atom,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^{10}$  and  $R^{11}$  each independently represents

- 5           a hydrogen atom,
- an alkyl group,
- a hydroxyalkyl group,
- a hydroxyalkylcarbonyl group,
- a hydroxyalkylsulfonyl group,
- 10          a formyl group,
- a formylalkyl group,
- a formylalkylcarbonyl group,
- a formylalkylsulfonyl group,
- an alkylcarbonyl group,
- 15          an alkylsulfonyl group,
- an alkylcarbonylalkyl group,
- an alkylsulfonylalkyl group,
- a carboxyl group,
- a carboxyalkyl group,
- 20          a carboxyalkylcarbonyl group,
- a carboxyalkylsulfonyl group,
- a carboxyalkylcarbonylalkyl group,
- a carboxyalkylsulfonylalkyl group,
- an alkoxyalkyl group,
- 25          an alkoxycarbonyl group,
- an alkoxycarbonylalkyl group,

an alkoxy-carbonylalkylcarbonyl group,

an alkoxy-carbonylalkylsulfonyl group,

an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents,

5        an aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents,

an aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents,

10        an aminocarbonylalkyl group which may have, at the amino moiety thereof, one or two substituents

an alkylsulfonylaminocarbonylalkyl group which may have, at the amino moiety thereof, one substituent,

an arylsulfonylaminocarbonyl group which may have, at the amino moiety thereof, one substituent,

15        an aminosulfonylalkyl group which may have, at the amino moiety thereof, one or two substituents,

a cyanoalkyl group,

an alkoxyalkylaminocarbonylalkyl group which may have, at the amino moiety thereof, one substituent,

20        an alkylcarbonyloxyalkyl, or

a group  $A^2-B^2-$  (in which  $A^2$  represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, and  $B^2$  represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a group  $-O-(C_{1-6}$  al-

25

kylene), a group -COO-(C<sub>1-6</sub> alkylene), a group -NHCO- or a group -NHCO-(C<sub>1-6</sub> alkylene group),

each of R<sup>3</sup> and R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup>, and R<sup>10</sup> and R<sup>11</sup> may be coupled together with a carbon atom which constitutes the ring and represent a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent, R<sup>9</sup> and R<sup>12</sup> each independently represents:

- 10        a hydrogen atom,
- an alkyl group,
- a hydroxyalkyl group,
- a hydroxyalkylcarbonyl group,
- a hydroxyalkylsulfonyl group,
- 15        an alkoxyl group,
- an alkoxyalkyl group,
- an alkoxyalkylcarbonyl group,
- an alkoxyalkylsulfonyl group,
- a formyl group,
- 20        a formylalkyl group,
- a formylalkylcarbonyl group,
- a formylalkylsulfonyl group,
- an alkylcarbonyl group,
- an alkylcarbonylalkyl group,
- 25        an alkylsulfonyl group,
- an alkylsulfonylalkyl group,

- a carboxyalkyl group,
- a carboxyalkylcarbonyl group,
- a carboxyalkylsulfonyl group,
- a carboxyalkylcarbonylalkyl group,
- 5 a carboxyalkylsulfonylalkyl group,
- an alkoxycarbonyl group,
- an alkoxycarbonylalkyl group,
- an alkoxycarbonylalkylcarbonyl group,
- an alkoxycarbonylalkylsulfonyl group,
- 10 an amino group which may have one or two substituents,
- an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents
- an aminoalkyloxy group which may have, at the amino moiety thereof, one or two substituents,
- 15 an aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminoalkyloxycarbonyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents,
- 20 an aminocarbonylalkyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminocarbonyloxyalkyl group which may have, at the amino moiety thereof, one or two substituents,
- 25 an alkylsulfonylaminocarbonylalkyl group which may have, at the amino moiety thereof, one substituent,



an arylsulfonylaminocarbonyl group which may have, at the amino moiety thereof, one substituent,

an aminosulfonylalkyl group which may have, at the amino moiety thereof, one or two substituents,

5 a cyanoalkyl group,

an alkoxyalkylaminocarbonylalkyl group which may have, at the amino moiety thereof, one substituent, or

an alkylcarbonyloxyalkyl,

$R^9$  and  $R^7$  or  $R^8$  may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which  $R^9$  has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent,

$R^{12}$  and  $R^{10}$  or  $R^{11}$  may be coupled together with a carbon atom constituting the ring and a nitrogen atom to which  $R^{12}$  has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent,

a, b, d, e and g each independently stands for an integer of 0 or 1, c stands for an integer of 0 to 3, and f, h and i each independently represents an integer of 1 to 3, with the proviso that the sum of a, b and c stands for an integer of 2 or 3, the sum of d and e stands for an integer of 0 or 1 and the sum of f, g and h stands for an integer of 3 to 5),

$Q^A$  represents an arylalkenyl group which may have a

substituent, a heteroarylalkenyl group which may have a substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent, a saturated or unsaturated tricyclic fused ring group which may have a substituent, a group  $\text{Ar-C(H)=N-}$  (in which, Ar represents an aryl group which may have a substituent), or a group  $\text{Het-C(H)=N-}$  (in which, Het represents a heteroaryl group which may have a substituent), and

$\text{T}^1$  represents a carbonyl group,

10 a group  $-\text{CH(R}^{13})-$

(in which  $\text{R}^{13}$  represents a hydrogen atom, an alkyl group, a hydroxyalkyl group having the hydroxyl group which may be protected, an alkoxyalkyl group, a carboxyalkyl group, an alkoxycarbonylalkyl group, an aryl group, an aralkyl group, 15 a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent (protecting group)), or

a group  $-\text{C(=NOR}^{14})-$  or  $-\text{C(=N-NHR}^{14'})-$

(in which  $\text{R}^{14}$  and  $\text{R}^{14'}$  each independently represents a hydrogen atom, an alkyl group, a carboxyalkyl group, an alkoxy-carbonyl group, an aryl group, an aralkyl group, a heteroaryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent.

25 The present invention also provides a pharmaceutical comprising as an effective ingredient a sulfonyl derivative

represented by the above-described formula (I) or salt thereof, or a solvate thereof.

The present invention also provides a pharmaceutical composition comprising a sulfonyl derivative represented by the above-described formula (I) or salt thereof, or a solvate thereof and a pharmaceutically acceptable carrier.

The present invention also provides use of a sulfonyl derivative represented by the above-described formula (I) or salt thereof, or a solvate thereof as a pharmaceutical.

The present invention also provides a method for treating diseases caused by FXa, blood coagulating diseases and various diseases due to thrombosis or embolism, which comprises administering a sulfonyl derivative represented by the above-described formula (I) or salt thereof, or a solvate thereof.

#### **Best Modes for Carrying Out the Invention**

A description will next be made of the substituents in the sulfonyl group derivative of the formula (I) according to the present invention.

<About group Q<sup>A</sup>>

Q<sup>A</sup> represents an arylalkenyl group which may have a substituent, a heteroarylalkenyl group which may have a substituent, a saturated or unsaturated dicyclic fused ring group which may have a substituent, a saturated or unsaturated tricyclic fused ring group which may have a substituent-

ent, a group  $\text{Ar-C(H)=N-}$  (in which, Ar represents an aryl group which may have a substituent), or a group  $\text{Het-C(H)=N-}$  (in which, Het represents a heteroaryl group which may have a substituent).

5           In the group  $\text{Q}^{\text{A}}$ , the term "arylalkenyl group which may have a substituent" means a group composed of an aryl group and a linear, branched or cyclic  $\text{C}_{2-6}$  alkenylene group. Examples of the aryl group include phenyl, naphthyl, anthryl and phenanthryl group. Examples of the arylalkenyl group  
10       include phenylethenyl group.

          The "heteroarylalkenyl group which may have a substituent" means a group composed of a heteroaryl group and a linear, branched or cyclic  $\text{C}_{2-6}$  alkenylene group. The "heteroaryl group" means an aromatic monovalent group hav-  
15       ing at least one hetero atom and examples include pyridyl, furyl and thienyl groups. Examples of the heteroarylalkenyl group include pyridylethenyl group.

          The "saturated or unsaturated, dicyclic or tricyclic fused ring group which may have a substituent" means: 1) a  
20       group obtained by the condensation of saturated or unsaturated 5- or 6-membered cyclic hydrocarbon groups which may have a substituent, 2) a group obtained by the condensation of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a saturated or unsaturated 5- or 6-membered heterocyclic group  
25       which may have a substituent and 3) a group obtained by the

condensation of saturated or unsaturated 5- or 6-membered heterocyclic groups which may have a substituent.

Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl groups. When the group has plural structural isomers as the cyclopentenyl group, they are all embraced in it.

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has plural structural isomers as the pyranyl, it is to be noted that they are all embraced in it.

Examples of the group 1) include indenyl, indanyl, naphthyl, tetrahydronaphthyl, anthryl and phenanthryl; those of the group 2) include benzofuranyl, benzothienyl, indolyl, indolinyl, quinolyl, benzodiazinyl, tetrahydroisoquinolyl, benzothiazolyl, tetrahydrobenzothiazolyl and

isoindolyl; and those of the group 3) include naphthyridinyl, tetrahydrothienopyridyl, tetrahydrothiazolopyridyl, tetrahydropyridopyridyl, thiazolopyridazinyl, tetrahydrothiazolopyridazinyl, pyrrolopyridyl, tetrahydro-  
 5 pyrrolopyridyl, dihydropyridoquinazolinyl, pyridopyrimidinyl, tetrahydropyridopyrimidinyl, pyranothiazolyl, dihydropyranothiazolyl, furopyridyl, tetrahydrofuropyridyl, oxazolopyridyl, and tetrahydrooxazolopyridyl.

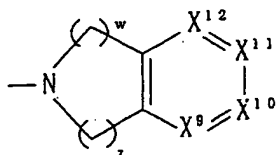
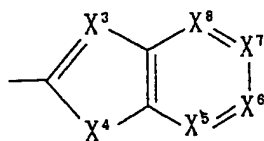
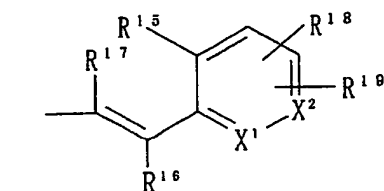
The aryl group in the group  $\text{Ar-C(H)=N}$  (wherein Ar represents an aryl group which may have a substituent) means  
 10 an aryl group similar to that described above. The group  $\text{Ar-C(CH)=N-}$  means a group composed of a phenyl group which may have a substituent and a group  $\text{-C(H)=N-}$  or the like.

The heteroaryl group in the group  $\text{Het-C(H)=N-}$  (wherein Het represents a heteroaryl group which may have a substituent) means a heteroaryl group similar to that described above. The group  $\text{Het-C(H)=N-}$  means a group composed of a pyridyl group which may have a substituent and a  
 15 group  $\text{Het-C(H)=N-}$ .  
 20

Each of the arylalkenyl group, heteroarylalkenyl group, saturated or unsaturated dicyclic fused ring group, saturated or unsaturated tricyclic fused ring group, the group  $\text{Ar-C(H)=N-}$  and the group  $\text{Het-C(H)=N-}$  may have one or  
 25 two substituents. Examples of the substituent include a hydroxyl group, halogen atoms such as fluorine, chlorine,

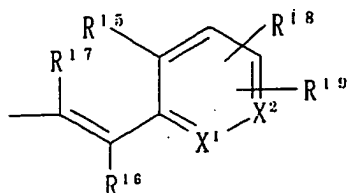
bromine and iodine, halogenomethyl groups having 1 to 3  
 halogen atoms substituted, an amino group, a cyano group,  
 an aminomethyl group, an amidino group, a hydroxyamidino  
 group, linear, branched or cyclic C<sub>1-6</sub> alkyl groups (ex.  
 5 methyl and ethyl), linear, branched or cyclic C<sub>1-6</sub> alkoxy  
 groups (ex. methoxyl and ethoxyl), linear, branched or cy-  
 clic C<sub>2-7</sub> alkoxy-carbonylamidino groups (ex. methoxycarbonyl-  
 amidino and ethoxycarbonylamidino), linear, branched or cy-  
 clic C<sub>2-6</sub> alkenyl groups (ex. vinyl and allyl), linear,  
 10 branched or cyclic C<sub>2-6</sub> alkynyl groups (ex. ethynyl and pro-  
 pynyl), linear, branched or cyclic C<sub>2-6</sub> alkoxy-carbonyl  
 groups (ex. methoxycarbonyl and ethoxycarbonyl) and amino-  
 carbonyl groups.

More specifically, the group Q<sup>A</sup> represents any one of  
 15 the following groups.



A description will next be made of the substituent in these groups.

In the group



- 5  $R^{15}$  represents a hydrogen atom, a hydroxyl group, a nitro group, a cyano group, a halogen atom, an alkyl group, a hydroxyalkyl group, an alkoxyl group, an alkoxyalkyl group, a carboxyl group, a carboxyalkyl group, an alkylcarbonyl group, an alkoxycarbonyl group, an alkoxycarbonyalkyl group, an alkylcarbonyloxy group or a group  $A^3-B^3$
- 10 (wherein,  $A^3$  represents an amino group which may have one or two substituents, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and  $B^3$  represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylencarbonyloxy group).
- 15

20 In  $R^{15}$ , examples of the halogen atom include fluorine, chlorine, bromine and iodine.

Examples of the alkyl group include linear, branched or cyclic  $C_{1-6}$  alkyl groups such as methyl, ethyl, isopropyl and cyclopropyl.



The "hydroxyalkyl group" means a group composed of a hydroxyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples of the alkylene group include methylene, ethylene, trimethylene, propylene and cyclohexylene. Examples of the hydroxyalkyl group include hydroxymethyl and hydroxyethyl.

The "alkoxyl group" means a group formed of the above-described C<sub>1-6</sub> alkyl group and an oxygen atom. Examples include methoxyl, ethoxyl and isopropoxyl.

10 The "alkoxyalkyl group" means a group formed of a linear, branched or cyclic C<sub>1-6</sub> alkoxyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include methoxymethyl, methoxyethyl and ethoxymethyl.

15 The "carboxyalkyl group" means a group formed of a carboxyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include carboxymethyl and carboxyethyl.

20 The "alkylcarbonyl group" means a group formed of a linear, branched or cyclic C<sub>1-6</sub> alkyl group and a carbonyl group. Examples include methylcarbonyl and ethylcarbonyl.

The "alkoxycarbonyl group" means a group formed of a linear, branched or cyclic alkoxyl group and a carbonyl group. Examples include methoxycarbonyl and ethoxycarbonyl.

25 The "alkoxycarbonylalkyl group" means a group formed of a linear, branched or cyclic C<sub>2-7</sub> alkoxycarbonyl group

and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include methoxycarbonylethyl and ethoxycarbonylmethyl.

The "alkylcarbonyloxy group" means a group formed of a linear, branched or cyclic C<sub>2-7</sub> alkylcarbonyl group and an oxygen atom. Examples include methylcarbonyloxy, ethylcarbonyloxy and isopropylcarbonyloxy.

In the group A<sup>3</sup>-B<sup>3</sup>-, A<sup>3</sup> means an amino group which may have one or two substituents, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent.

When A<sup>3</sup> means an amino group which may have one or two substituents, B<sup>3</sup> represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylencarbonyloxy group. The group A<sup>3</sup>-B<sup>3</sup>- therefore means, for example, a group as shown in the following class (A).

Class (A):

- an amino group which may have one or two substituents,
- an aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminocarbonylalkyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminocarbonylalkyloxy group which may have, at the

amino moiety thereof, one or two substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents and

an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, one or two substituents.

A description will next be made of the groups shown in Class (A).

The "aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents" means a group formed of an amino group which may have one or two substituents and a carbonyl group.

The "aminoalkyl group which may have, at the amino moiety thereof, one or two substituents" means a group formed of an amino group which may have one or two substituents and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples of the aminoalkyl group include aminomethyl and aminoethyl.

The "aminocarbonylalkyl group which may have, at the amino moiety thereof, one or two substituents" means a group formed of the above-described aminocarbonyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples of the aminocarbonylalkyl group include aminocarbonylmethyl and aminocarbonylethyl.

The "aminocarbonylalkyloxy group which may have, at the amino moiety, one or two substituents" means a group formed of the above-described aminocarbonylalkyl group which

may have a substituent and an oxygen atom. Examples of the aminocarbonylalkyloxy group include aminocarbonylmethoxyl and aminocarbonylethoxyl.

5 The "aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents" means a group formed of the above-described aminoalkyl group which may have a substituent and a carbonyl group. Examples of the aminoalkylcarbonyl group include aminomethylcarbonyl and aminoethylcarbonyl.

10 The "aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, one or two substituents" means a group formed of the above-described aminoalkylcarbonyl group which may have a substituent and an oxygen atom. Examples of the aminoalkylcarbonyloxy group include aminomethylcarbonyloxy and aminoethylcarbonyloxy.

15 Examples of the substituent which can be substituted for an amino group (moiety) include those as shown in the following Class (1).

Class (1):

- 20 an alkyl group,  
an alkenyl group,  
a halogenoalkyl group,  
a halogenoalkenyl group,  
a hydroxyalkyl group,  
25 a hydroxyalkylcarbonyl group,  
a hydroxyalkylsulfonyl group,

- an alkoxyl group,
- an alkoxyalkyl group,
- an alkoxyalkylcarbonyl group,
- an alkoxyalkylsulfonyl group,
- 5 a formyl group,
- a formylalkyl group,
- a formylalkylcarbonyl group,
- a formylalkylsulfonyl group,
- an alkylcarbonyl group,
- 10 an alkylcarbonylalkyl group,
- an alkylsulfonyl group,
- an alkylsulfonylalkyl group,
- a carboxyalkyl group,
- a carboxyalkylcarbonyl group,
- 15 a carboxyalkylsulfonyl group,
- a carboxyalkylcarbonylalkyl group,
- a carboxyalkylsulfonylalkyl group,
- an alkoxy carbonyl group,
- an alkoxy carbonylalkyl group,
- 20 an alkoxy carbonylalkylcarbonyl group,
- an alkoxy carbonylalkylsulfonyl group,
- a trifluoromethylsulfonyloxyalkenyl group and
- a group  $a^3-b^3-$

(wherein  $a^3$  represents a saturated or unsaturated 5- or 6-  
 25 membered cyclic hydrocarbon group or saturated or unsaturated 5- or 6-membered heterocyclic group which may have

one to three substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, an alkoxyl group, an alkyl group, a cyano group, a nitro group, a carboxyl group, an alkoxycarbonyl group and an aminocarbonyl group; and

$b^3$  represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group, an alkylenecarbonyloxy group, an alkyleneaminocarbonyl group, an alkyleneaminocarbonylalkyl group, an alkyleneaminosulfonyl group or an alkyleneaminosulfonylalkyl group.

The substituents which can be substituted for an amino group (moiety) in Class (1) will next be described.

The "alkyl group" means a linear, branched or cyclic  $C_{1-6}$  alkyl group.

The "alkenyl group" means a linear, branched or cyclic  $C_{2-6}$  alkenyl group. Examples include vinyl and allyl.

The "halogenoalkyl group" means a group formed of a halogen atom and a linear, branched or cyclic  $C_{1-6}$  alkylene group. Examples include chloromethyl and bromoethyl.

The "halogenoalkenyl group" means a group formed of a halogen atom and a linear or branched  $C_{2-6}$  alkenylene group. Examples include chlorovinyl and bromoallyl groups. There is no particular limitation on the position of a double bond.

The "hydroxyalkyl group" means a group formed of a hy-

droxyl group and a linear, branched or cyclic C<sub>2-6</sub> alkylene group. Examples include hydroxyethyl and hydroxypropyl.

The "hydroxyalkylcarbonyl group" means a group formed of the above-described hydroxyalkyl group and a carbonyl group. Examples include hydroxymethylcarbonyl and hydroxyethylcarbonyl.

The "hydroxyalkylsulfonyl group" means a group formed of the above-described hydroxyalkyl group and a sulfonyl group. Examples include hydroxymethylsulfonyl and hydroxyethylsulfonyl. The "alkoxyl group" means a linear, branched or cyclic C<sub>1-6</sub> alkoxyl group.

The "alkoxyalkyl group" means a group formed of a linear, branched or cyclic C<sub>1-6</sub> alkoxyl group and a linear, branched or cyclic C<sub>2-6</sub> alkylene group. Examples include methoxyethyl, ethoxyethyl and methoxypropyl.

The "alkoxyalkylcarbonyl group" means a group formed of the above-described alkoxyalkyl group and a carbonyl group. Examples include methoxyethylcarbonyl and ethoxymethylcarbonyl.

The "alkoxyalkylsulfonyl group" means a group formed of the above-described alkoxyalkyl group and a sulfonyl group. Examples include methoxyethylsulfonyl and ethoxymethylsulfonyl.

The "formylalkyl group" means a group formed of a formyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include formylmethyl and formylethyl.

The "formylalkylcarbonyl group" means a group formed of the above-described formylalkyl group and a carbonyl group. Examples include formylmethylcarbonyl and formylethylcarbonyl.

5       The "formylalkylsulfonyl group" means a group formed of the above-described formylalkyl group and a sulfonyl group. Examples include formylmethylsulfonyl and formylethylsulfonyl.

10       The "alkylcarbonyl group" means a group formed of a linear, branched or cyclic C<sub>1-6</sub> alkyl group and a carbonyl group. Examples include methylcarbonyl and ethylcarbonyl.

15       The "alkylcarbonylalkyl group" means a group formed of the above-described alkylcarbonyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include methylcarbonylmethyl and ethylcarbonylmethyl.

      The "alkylsulfonyl group" means a group formed of the above-described alkyl group and a sulfonyl group. Examples include methylsulfonyl and ethylsulfonyl.

20       The "alkylsulfonylalkyl group" means a group formed of the above-described alkylsulfonyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include methylsulfonylmethyl and ethylsulfonylmethyl.

25       The "carboxyalkyl group" means a group composed of a carboxyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group.

      The "carboxyalkylcarbonyl group" means a group formed



of the above-described carboxyalkyl group and a carbonyl group. Examples include carboxymethylcarbonyl and carboxyethylcarbonyl.

5 The "carboxyalkylsulfonyl group" means a group formed of the above-described carboxyalkyl group and a sulfonyl group. Examples include carboxymethylsulfonyl and carboxyethylsulfonyl.

10 The "carboxyalkylcarbonylalkyl group" means a group formed of the above-described carboxyalkylcarbonyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include carboxymethylcarbonylmethyl and carboxyethylcarbonylmethyl.

15 The "carboxyalkylsulfonylalkyl group" means a group formed of the above-described carboxyalkylsulfonyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include carboxymethylsulfonylmethyl and carboxyethylsulfonylmethyl.

20 The "alkoxycarbonyl group" means a group formed of a linear, branched or cyclic C<sub>1-6</sub> alkoxyl and a carbonyl group.

The "alkoxycarbonylalkyl group" means a group formed of the above-described alkoxycarbonyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group.

25 The "alkoxycarbonylalkylcarbonyl group" means a group formed of the above-described alkoxycarbonylalkyl group and a carbonyl group. Examples include methoxycarbonylethyl-

carbonyl and ethoxycarbonylmethylcarbonyl.

The "alkoxycarbonylalkylsulfonyl group" means a group of the above-described alkoxycarbonylalkyl group and a sulfonyl group. Examples include methoxycarbonylethylsulfonyl and ethoxycarbonylmethylsulfonyl.

The "trifluoromethylsulfonyloxyalkenyl group" means a group formed of a trifluoromethylsulfonyloxy group and a linear or branched C<sub>2-6</sub> alkenylene group. Examples include trifluoromethylsulfonyloxyvinyl and trifluoromethylsulfonyloxyallyl.

In the group a<sup>3</sup>-b<sup>3</sup>-, a<sup>3</sup> represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent such as a halogen atom. Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. Where the group has, as the cyclopentenyl, plural structural isomers, they are all embraced in it.

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxa-

zolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has, as the pyranyl, plural structural isomers, they are all embraced in it.

$b^3$  represents a single bond or a divalent group such as carbonyl, alkylene, carbonylalkyl, carbonylalkyloxy, alkylenecarbonyloxy, alkyleneaminocarbonyl, alkyleneaminocarbonylalkyl, alkyleneaminosulfonyl or alkyleneaminosulfonylalkyl. The "alkylene group" means a linear, branched or cyclic  $C_{1-6}$  alkylene group.

The "carbonylalkyl group" means a group formed of a carbonyl group and a linear, branched or cyclic  $C_{1-6}$  alkylene group. Examples include carbonylmethyl and carbonylethyl.

The "carbonylalkyloxy group" means a group formed of the above-described carbonylalkyl group and an oxygen atom. Examples include carbonylmethoxy and carbonylethoxy.

The "alkylenecarbonyloxy group" means a group formed of a linear, branched or cyclic  $C_{1-6}$  alkylene group, a carbonyl group and an oxygen atom. Examples include methylenecarbonyloxy and ethylenecarbonyloxy.

The "alkyleneaminocarbonyl group" means a group formed of a linear, branched or cyclic  $C_{1-6}$  alkylene group, an

imino group and a carbonyl group. Examples include methyleneaminocarbonyl and ethyleneaminocarbonyl.

The "alkyleneaminocarbonylalkyl group" means a group formed of the above-described alkyleneaminocarbonyl and a  
 5 linear, branched or cyclic C<sub>1-6</sub> alkylene. Examples include methyleneaminocarbonylmethyl and ethyleneaminocarbonylmethyl.

The "alkyleneaminosulfonyl group" means a group formed of a linear, branched or cyclic C<sub>1-6</sub> alkylene group, an  
 10 imino group and a sulfonyl group. Examples include methyleneaminosulfonyl and ethyleneaminosulfonyl.

The "alkyleneaminosulfonylalkyl group" means a group formed of the above-described alkyleneaminosulfonyl and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples  
 15 include methyleneaminosulfonylmethyl and ethyleneaminosulfonylmethyl.

A description will next be made of the substituents which can be introduced into, as the above-described a<sup>3</sup>, a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or saturated or unsaturated 5- or 6-membered heterocyclic group. Examples include halogen atoms, an  
 20 alkoxyl group, an alkyl group, an alkoxycarbonyl and an aminocarbonyl group.

As the group a<sup>3</sup>-b<sup>3</sup>-, there exist various kinds according to the combination of a<sup>3</sup> and b<sup>3</sup>. Examples include:

a saturated or unsaturated, 5- or 6-membered cyclic

hydrocarbon group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and a carbonyl group,

5 a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent  
10 and a carbonylalkyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a carbonylalkyloxy group,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent  
15 and a alkylene carbonyloxy group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkyleneaminocarbonyl group,

20 a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkyleneaminocarbonylalkyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent  
25 and an alkyleneaminosulfonyl group,

a group formed of a saturated or unsaturated 5- or 6-

membered heterocyclic group which may have a substituent and an alkyleneaminosulfonylalkyl group, and the like.

In addition to the above-described Class (1), the following Class (2) can be given as examples of the substituent which can be substituted for the amino group (moiety).  
5 Class (2):

an amino group which may have one or two substituents selected from Class (1),

an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),  
10

an aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),

an aminocarbonylalkyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),  
15

an aminocarbonylalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),  
20

an aminocarbonylalkylsulfonyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),  
25

an aminosulfonyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),

an aminosulfonylalkyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),

an aminoalkylsulfonyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1),

an aminosulfonylalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1) and

an aminosulfonylalkylsulfonyl group which may have, at the amino moiety thereof, one or two substituents selected from Class (1).

A description will next be made of the substituents of Class (2).

The aminoalkyl, aminocarbonyl, aminocarbonylalkyl and aminoalkylcarbonyl groups in Class (2) have the same meanings as described above.

The "aminoalkyl group which may have a substituent at the amino moiety" means a group formed of an amino group which may have the above-described substituent and a linear, branched or cyclic C<sub>2-6</sub> alkylene group. Examples of the aminoalkyl group include aminoethyl and aminopropyl.

The "aminocarbonylalkylcarbonyl group which may have a

substituent at the amino moiety" means a group formed of an aminocarbonylalkyl group which may have the above-described substituent and a carbonyl group. Examples of the aminocarbonylalkylcarbonyl group include aminocarbonylmethylcarbonyl and aminocarbonylethylcarbonyl.

The "aminocarbonylalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of an aminocarbonylalkyl group which may have the above-described substituent and a sulfonyl group. Examples of the aminocarbonylalkylsulfonyl group include aminocarbonylmethylsulfonyl and aminocarbonylethylsulfonyl.

The "aminosulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of an amino group which may have the above-described substituent and a sulfonyl group.

The "aminosulfonylalkyl group which may have, at the amino moiety thereof, a substituent" means a group formed of an aminosulfonyl group which may have the above-described substituent and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples of the aminosulfonylalkyl group include aminosulfonylmethyl and aminosulfonylethyl.

The "aminoalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of an aminoalkyl group which may have the above-described substituent and a sulfonyl group. Examples of the aminoalkylsulfonyl group include aminomethylsulfonyl and amino-



ethylsulfonyl.

The "aminosulfonylalkylcarbonyl group which may have, at the amino moiety thereof, a substituent" means a group formed of an aminosulfonylalkyl group which may have the  
5 above-described substituent and a carbonyl group. Examples of the aminosulfonylalkylcarbonyl group include aminosulfonylmethylcarbonyl and aminosulfonylethylcarbonyl.

The "aminosulfonylalkylsulfonyl group which may have, at the amino moiety thereof, a substituent" means a group  
10 formed of an aminosulfonylalkyl group which may have the above-described substituent and a sulfonyl group. Examples of the aminosulfonylalkylsulfonyl group include aminosulfonylmethylsulfonyl and aminosulfonylethylsulfonyl.

A<sup>3</sup> also represents a saturated or unsaturated 5- or 6-  
15 membered cyclic hydrocarbon group or heterocyclic group which may have a substituent. Examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl groups.  
20 Where the group has plural structural isomers as the cyclopentenyl group, they are all embraced in it.

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero  
atom. Examples of the hetero atom include oxygen, nitrogen  
25 and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl,

thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazoliny, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triadinyl. Where the group has plural structural isomers as pyranyl, they are all embraced in it.

When  $A^3$  represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent,  $B^3$  represents a single bond, a carbonyl group, an alkylene group, a carbonylalkyl group, a carbonylalkyloxy group or an alkylenecarbonyloxy group. Accordingly, the group  $A^3-B^3-$ , for example, represents a group as shown in the following Class (B):

Class (B):

a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and a carbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group

which may have a substituent, a carbonyl group and an alkylene group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group, an alkylene group and an oxygen atom,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group and a carbonyl group,

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group, a carbonyl group and an oxygen atom, and the like.

A description will next be made of the groups shown in Class (B).

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent and a carbonyl group, examples of the group formed of the cyclic hydrocarbon group and a carbonyl group include cyclopentylcarbonyl and phenylcarbonyl; while those of the group formed of the heterocyclic group and a carbonyl group include furylcarbonyl, thienylcarbonyl and pyridylcarbonyl groups.

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic

group which may have a substituent and an alkylene group, the "group formed of a cyclic hydrocarbon group and an alkylene group" means a group formed of the above-described cyclic hydrocarbon group and C<sub>1-6</sub> alkylene group, for example, cyclohexylmethyl and benzyl, while the "group formed of a heterocyclic group and an alkylene group" means a group formed of the above-described heterocyclic group and linear, branched or cyclic C<sub>1-6</sub> alkylene group, for example, furylmethyl, thienylethyl and pyridylpropyl.

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, a carbonyl group and an alkylene group, the "group formed of a cyclic hydrocarbon group, a carbonyl group and an alkylene group" means a group formed of the above-described cyclic hydrocarbon group, a carbonyl group and the above-described linear, branched or cyclic C<sub>1-6</sub> alkylene group, for example, cyclopentadienylcarbonylmethyl and phenylcarbonylethyl, while the "group formed of a heterocyclic group, a carbonyl group and an alkylene group" means a group formed of the above-described heterocyclic group, a carbonyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group, for example, furylcarbonylmethyl, thienylcarbonylethyl and pyridylcarbonylpropyl.

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic

group which may have a substituent, a carbonyl group, an alkylene group and an oxygen atom, the "group formed of a cyclic hydrocarbon group, a carbonyl group, an alkylene group and an oxygen atom" means a group composed of the above-described group, which is composed of a cyclic hydrocarbon group, carbonyl group and alkylene group, and an oxygen atom, for example, cyclopentylcarbonylmethoxy and phenylcarbonylethoxy, while the "group formed of a heterocyclic group, a carbonyl group, an alkylene group and an oxygen atom" means a group composed of the above-described group, which is composed of a heterocyclic group, a carbonyl group and an alkylene group, and an oxygen atom, for example, furylcarbonylmethoxy, thienylcarbonylethoxy and pyridylcarbonylpropoxy.

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group and a carbonyl group, "the group formed of a cyclic hydrocarbon group, an alkylene group and a carbonyl group" means a group composed of the above-described group, which is formed of a cyclic hydrocarbon group and an alkylene group, and a carbonyl group, for example, cyclohexylmethylcarbonyl and phenylethylcarbonyl, while "the group formed of a heterocyclic group, an alkylene group and a carbonyl group" means a group composed of the above-described group, which is formed of a heterocyclic group and an alkylene group,

and a carbonyl group, for example, furylmethylcarbonyl, thienylethylcarbonyl and pyridylpropylcarbonyl.

In the group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group which may have a substituent, an alkylene group, a carbonyl group and an oxygen atom, "the group formed of a cyclic hydrocarbon group, an alkylene group, a carbonyl group and an oxygen atom" means a group composed of the above-described group, which is formed of a cyclic hydrocarbon group, an alkylene group and a carbonyl group, and an oxygen atom, for example, cyclohexadienylmethylcarbonyloxy and phenylethylcarbonyloxy, while "the group formed of a heterocyclic group, an alkylene group, a carbonyl group and an oxygen atom" means a group composed of the above-described group, which is formed of a heterocyclic group, an alkylene group and a carbonyl group, and an oxygen atom such as furylmethylcarbonyloxy, thienylethylcarbonyloxy and pyridylpropylcarbonyloxy.

As examples of a substituent which can be substituted for the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group or heterocyclic group, those as shown in Class (3) can be given. The number of the substituents which can be replaced is 1 to 3.

Class (3):

a hydroxyl group,

an alkyl group,

an alkoxyl group,  
a hydroxyalkyl group,  
an alkoxyalkyl group,  
a halogen atom,  
5 a cyano group,  
a nitro group,  
a carboxyl group,  
an alkoxycarbonyl group,  
a formyl group,  
10 a heteroaryl group,  
a heteroarylalkyl group,  
an alkylimino group,  
an amidino group,  
a guanidino group,  
15 an amino(hydroxyimino)alkyl group,  
an amino(alkoxyimino)alkyl group,  
an amino(aryloxyimino)alkyl group,  
an amino group which may have one or two substituents,  
an aminocarbonyl group which may have, at the amino  
20 moiety thereof, one or two substituents,  
an aminocarbonylalkyl group which may have, at the  
amino moiety thereof, one or two substituents,  
an aminocarbonylalkyloxy group which may have, at the  
amino moiety thereof, one or two substituents,  
25 an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents,

an aminoalkyloxy group which may have, at the amino moiety thereof, one or two substituents,

an aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents,

5 an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, one or two substituents, and an oxygen atom.

A description will next be made of the substituents which can be replaced for the saturated or unsaturated 5-  
10 or 6-membered cyclic hydrocarbon or heterocyclic group in Class (3).

The alkyl group, alkoxyl group, hydroxyalkyl group, alkoxyalkyl group, halogen atom, alkoxycarbonyl group, aminocarbonyl group which may have, at the amino moiety  
15 thereof, one or two substituents, aminoalkyl group which may have, at the amino moiety thereof, one or two substituents, aminocarbonylalkyl group which may have, at the amino moiety thereof, one or two substituents, aminocarbonylalkyloxy group which may have, at the amino moiety thereof, one  
20 or two substituents, aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents, and aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, one or two substituents have the same meanings as described above.

25 The "heteroaryl group" means a monovalent aromatic group having at least one hetero atom. Examples include



pyridyl, furyl and thienyl.

The "heteroarylalkyl group" means a group formed of the above-described heteroaryl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group. Examples include pyridyl-  
5 methyl, furylethyl and thienylmethyl.

The "alkylimino group" means a divalent group formed of a linear, branched or cyclic C<sub>1-6</sub> alkyl group and a nitrogen atom. Examples include methylimino and ethylimino.

The "amino(hydroxyimino)alkyl group" means a group  
10 having amino and hydroxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C<sub>1-6</sub> alkyl group. Examples include amino(hydroxyimino)methyl and amino(hydroxyimino)ethyl.

The "amino(alkoxyimino)alkyl group" means a group hav-  
15 ing amino and alkoxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C<sub>1-6</sub> alkyl group. Here, the "alkoxyimino group" means a divalent group formed of the above-described alkoxyl group and an imino group. Examples of the amino(alkoxyimino)alkyl group include  
20 amino(methoxyimino)methyl and amino(ethoxyimino)methyl.

The "amino(aryloxyimino)alkyl group" means a group having amino and aryloxyimino groups bonded to the same carbon atom of a linear, branched or cyclic C<sub>1-6</sub> alkyl group. Here, the "aryloxyimino group" means a divalent  
25 group formed of aryl and imino groups. Examples of the aryl group usable here include phenyl, naphthyl, anthryl

and phenanthryl. Examples of the amino(aryloxyimino)alkyl group include amino(phenoxyimino)methyl and amino(naphthyloxyimino)methyl.

5 The "aminoalkyloxy group which may have, at the amino moiety thereof, one or two substituents" means a group formed of an amino group having a substituent, a linear, branched or cyclic C<sub>2-6</sub> alkylene group and an oxygen atom. Examples of the aminoalkyloxy group include aminoethyloxy and aminopropyloxy. Examples of the group which can be  
10 substituted for the amino moiety include those exemplified above.

In the case of the cyclic hydrocarbon group, an oxygen atom can serve as a substituent when the corresponding keto compound is formed, while, in the case of the heterocyclic  
15 group or dicyclic or tricyclic fused ring group, an oxygen atom can serve as a substituent when the oxygen atom is bonded to a nitrogen or sulfur atom forming the ring and the corresponding N-oxide or S-oxide or keto compound is formed.

20 In the present invention, when R<sup>15</sup> is not coupled with R<sup>16</sup> or R<sup>17</sup> to form a C<sub>1-3</sub> alkylene or alkenylene group, preferred examples of R<sup>15</sup> include a hydrogen atom, an alkyl group, a hydroxyalkyl group and a group A<sup>3</sup>-B<sup>3</sup>-.

In R<sup>16</sup> and R<sup>17</sup>, examples of the halogen atom include  
25 fluorine, chlorine, bromine and iodine.

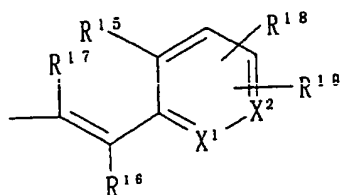
The "alkyl group" means a linear, branched or cyclic

C<sub>1-8</sub> alkyl group. Examples include methyl, ethyl, isopropyl, cyclopropyl, heptyl and octyl.

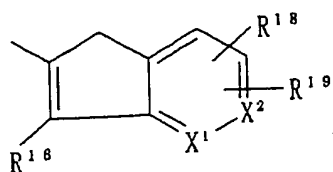
The "hydroxyalkyl group" means a group formed of a hydroxyl group and a linear, branched or cyclic C<sub>1-8</sub> alkylene group. Examples include hydroxymethyl and hydroxyethyl.

The "alkoxyalkyl group" means a group formed of the above-described alkyl group, an oxygen atom and a linear, branched or cyclic C<sub>1-8</sub> alkylene group. Examples include methoxymethyl, methoxyethyl and ethoxymethyl.

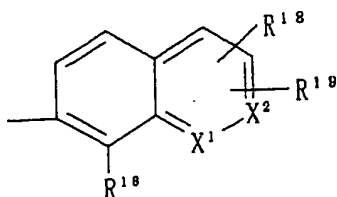
When R<sup>16</sup> or R<sup>17</sup> is coupled with R<sup>15</sup> to form a C<sub>1-3</sub> alkylene or alkenylene group, the following group:



means the following group:



15



or the like.

In the present invention, when R<sup>16</sup> or R<sup>17</sup> is not coupled with R<sup>15</sup> to form a C<sub>1-3</sub> alkylene or alkenylene group, a

hydrogen atom and alkyl group are preferred as  $R^{16}$  or  $R^{17}$ .

In the present invention, it is preferred that  $R^{15}$  and  $R^{16}$  or  $R^{17}$  are coupled together to form a  $C_{1-3}$  alkylene or alkenylene group.

5         $R^{18}$  and  $R^{19}$  each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxyl group, an alkenyl group, an alkynyl group which may be substituted with an alkylsilyl group as a protecting group, a trifluoromethyl group, 10 a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group (with the proviso that  $R^{18}$  and  $R^{19}$  do not represent a hydrogen atom at the same time).

15        In  $R^{18}$  and  $R^{19}$ , the halogen atom, halogenoalkyl group, alkyl group, alkoxyl group, alkenyl group and aminoalkyl group mean the same meaning as described above.

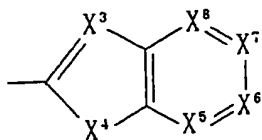
The "alkylaminoalkyl group" means a group having one or two linear, branched or cyclic alkyl groups substituted 20 with the amino group of the aminoalkyl moiety and examples include methylaminomethyl and ethylmethylaminomethyl.

The "alkynyl group which may be substituted with an alkylsilyl group as a protecting group" means an alkynyl group which may be substituted with an alkylsilyl group 25 such as trimethylsilyl, triethylsilyl, tertiary butyldimethylsilyl or dimethylphenylsilyl group as a protecting

group.

In the present invention, as  $R^{18}$  or  $R^{19}$ , a halogen atom and alkynyl group are preferred, with a hydrogen atom, chlorine atom, bromine atom and ethynyl group are particularly preferred.

$X^3$  in the group:



means a nitrogen atom or a group  $=C(R^{100})-$

(wherein,  $R^{100}$  represents a hydrogen atom, a halogen atom, an alkyl group, an alkoxy carbonyl group, an aralkyloxy carbonylalkyl group, an alkoxy carbonylalkyl group, a nitro group, an amino group which may have a protecting group or an aminoalkyl group which may have, at the amino moiety thereof, a protecting group).

The halogen atom, alkyl group, alkoxy carbonyl group, aryloxy carbonylalkyl group, alkoxy carbonylalkyl group, aryloxy carbonylalkyl group in  $R^{100}$  have the same meanings as described above, respectively. The amino group which may have a protecting group or aminoalkyl group which may have, at the amino moiety thereof, a protecting group mean amino group and aminoalkyl groups which may have an ordinarily known protecting group, respectively.

$X^4$  represents an oxygen atom, a sulfur atom or a group  $-N(R^{101})-$

(wherein  $R^{101}$  means a hydrogen atom, an alkyl group, an alkoxy carbonyl group, an aralkyloxy carbonyl group, an alkoxy carbonyl alkyl group, an alkylsulfonyl group or an arylsulfonyl group).

5       The alkyl group, alkoxy carbonyl group, aralkyloxy carbonyl group, alkoxy carbonyl alkyl group, alkylsulfonyl group and arylsulfonyl group in  $R^{101}$  have the same meanings as described above, respectively.

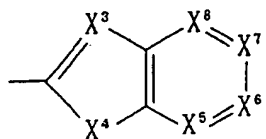
10        $X^5$  and  $X^8$  each independently represents a nitrogen atom or a group  $-C(R^{102})$  (wherein,  $R^{102}$  represents a hydrogen atom or a halogen atom) and the halogen atom in  $R^{102}$  has the same meaning as described above.

15        $X^6$  and  $X^7$  each independently represents a nitrogen atom or a group  $-C(R^{103})-$  (wherein  $R^{103}$  represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxy group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxy carbonylamidino group).

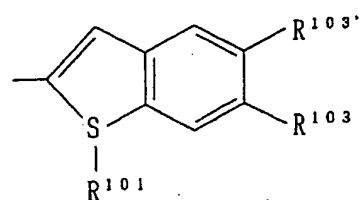
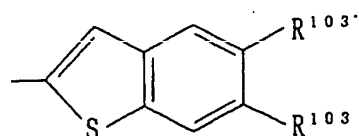
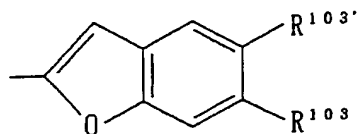
25       The halogen atom, halogenoalkyl group, alkyl group, alkoxy group, alkenyl group, alkynyl group which may be

substituted by an alkylsilyl group as a protecting group, aminoalkyl group, alkylaminoalkyl group, alkoxycarbonylamidino group in  $R^{103}$  have the same meanings as described above.

5 It is preferred that the group:



means any one of the following groups:



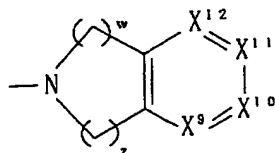
10 [wherein  $R^{101}$  and  $R^{103}$  have the same meanings as described above and  $R^{103'}$  means those similar to  $R^{103}$ ].

As  $R^{101}$ , a hydrogen atom is particularly preferred. It is preferred that either one of  $R^{103}$  and  $R^{103'}$  represents a halogen atom, an alkynyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group, with the halogen atom, ethynyl group, amidino group, hy-

15

droxyamidino group and methoxycarbonylamidino group being particularly preferred.

In the group:



5  $X^9$  and  $X^{12}$  each independently represents a nitrogen atom or a group  $-C(R^{104})-$

(wherein  $R^{104}$  represents a hydrogen atom or a halogen atom) and the halogen atom as  $R^{104}$  is similar to that described above.

10  $X^{10}$  and  $X^{11}$  each independently represents a nitrogen atom or

a group  $-C(R^{105})-$

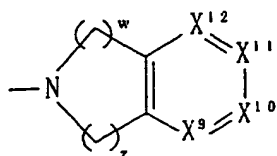
(wherein  $R^{105}$  represents a hydrogen atom, a hydroxyl group, a halogen atom, a halogenoalkyl group, an alkyl group, an alkoxy group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, a cyano group, an amino group, an aminoalkyl group, an alkylaminoalkyl group, an amidino group, a hydroxyamidino group or an alkoxycarbonylamidino group).

20 The halogen atom, halogenoalkyl group, alkyl group, alkoxy group, alkenyl group, alkynyl group which may be substituted by an alkylsilyl group as a protecting group, aminoalkyl group, alkylaminoalkyl group alkoxycarbonylam-

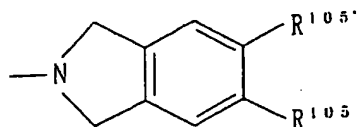


idino group in  $R^{105}$  have the same meanings as described above.

The group:



5 preferably represents the following group:



[wherein  $R^{105}$  has the same meanings as described above and  $R^{105'}$  is similar to that described as  $R^{105}$ ].

10 It is preferred that either one of  $R^{105}$  and  $R^{105'}$  represents a halogen atom, an alkynyl group, an amidino group, a hydroxyamidino group or an alkoxy-carbonylamidino group, with the halogen atom, ethynyl group, amidino group, hydroxyamidino group and methoxy-carbonylamidino group being particularly preferred.

15 <About the group  $Q^1$ >

$Q^1$  represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent, a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent, a saturated or unsaturated bicyclic fused ring group which may have a substituent, or a saturated or unsaturated tricyclic fused

20

ring group which may have a substituent.

Here, examples of the saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has plural structural isomers as cyclopentenyl, they are all embraced in it.

The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, pyrazinyl, tetrahydropyrazinyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, thiazolidinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyrimidinyl, tetrahydropyrimidinyl, pyridazinyl, tetrahydropyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, tetrazinyl, triazolyl and triazinyl. Where the group has plural structural isomers as pyranyl, they are all embraced in it.

The "saturated or unsaturated, dicyclic fused ring group which may have a substituent" or "saturated or unsaturated, tricyclic fused ring group which may have a substituent" has the same meaning as defined in the descrip-

tion of the group  $Q^A$ . More specifically, it means: 1) a group obtained by the condensation of saturated or unsaturated 5- or 6-membered cyclic hydrocarbon groups which may have a substituent, 2) a group obtained by the condensation of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and 3) a group obtained by the condensation of saturated or unsaturated 5- or 6-membered heterocyclic groups which may have a substituent. Examples of the group 1) include indenyl, indanyl, naphthyl, tetrahydronaphthyl, anthryl and phenanthryl; those of the group 2) include benzofuranyl, indolyl, indolinyl, quinolyl, benzodiazinyl, tetrahydroisoquinolyl, benzothiazolyl, tetrahydrothiazolyl and isoindolyl; and those of the group 3) include naphthyridinyl, furanopyridyl, thienopyridyl, tetrahydrothienopyridyl, pyrazolopyridyl, thiazolopyridyl, tetrahydrothiazolopyridyl, thiazolopyrazyl, tetrahydrothiazolopyrazyl, thiazolopyridazyl, tetrahydropyridopyridyl, thiazolopyridazinyl, tetrahydrothiazolopyridazinyl, pyrrolopyridyl, tetrahydropyrrolopyridyl, dihydropyridoquinazolinyl, pyridopyrimidinyl, tetrahydropyridopyrimidinyl, pyranothiazolyl, dihydropyranothiazolyl, furopyridyl, tetrahydrofuropyridyl, oxazolopyridyl and tetrahydrooxazolopyridyl.

Examples of the substituent which can be replaced for

the above-described saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group, saturated or unsaturated 5- or 6-membered heterocyclic group, saturated or unsaturated dicyclic fused ring group, or saturated or unsaturated tricyclic fused ring group include the groups shown in the below-described Class (4). The number of the replaceable substituents ranges from 1 to 7.

Class (4):

- a hydroxyl group,
- 10 an alkyl group,
- an alkenyl group,
- a halogenoalkyl group,
- a halogenoalkenyl group,
- an alkoxyl group,
- 15 a hydroxyalkyl group,
- an alkoxyalkyl group,
- a halogen atom,
- a cyano group,
- a nitro group,
- 20 a carboxyl group,
- an alkoxycarbonyl group,
- a formyl group,
- a heteroaryl group,
- a heteroarylalkyl group,
- 25 an alkylimino group,
- an alkylsulfonyl group,

- an amidino group,
- a guanidino group,
- an amino(hydroxyimino)alkyl group,
- an amino(alkoxyimino)alkyl group,
- 5 an amino(aryloxyimino)alkyl group,
- a hydroxyimino group,
- an alkoxyimino group,
- an aminoimino group which may have, at the amino moiety thereof, one or two substituents,
- 10 an amino group which may have one or two substituents,
- an aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminocarbonylalkyl group which may have, at the amino moiety thereof, one or two substituents,
- 15 an aminocarbonylalkyloxy group which may have, at the amino moiety thereof, one or two substituents,
- an aminosulfonyl group which may have, at the amino moiety thereof, one or two substituents,
- an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents,
- 20 an aminoalkyloxy group which may have, at the amino moiety thereof, one or two substituents,
- an aminoalkylcarbonyl group which may have, at the amino moiety thereof, one or two substituents,
- 25 an aminoalkylcarbonyloxy group which may have, at the amino moiety thereof, one or two substituents,

an oxygen atom,  
a trifluoromethylsulfonyloxy group,  
a trifluoromethylsulfonyloxyalkenyl group,  
a boric acid group ( $-B(OH_2)$ ),

5 a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have 1 to 3 substituents selected from the group consisting of halogen, hydroxyl, amino, alkoxyl, alkyl, cyano, nitro, carboxyl, alkoxycarbonyl, aminocarbonyl which may have, at the amino moiety thereof, one  
10 or two substituents, aminosulfonyl which may have, at the amino moiety thereof, one or two substituents, aminoalkyl which may have, at the amino moiety thereof, one or two substituents and trifluoromethyl, and saturated or unsaturated 5- or 6-membered heterocyclic group which may have 1  
15 to 3 substituents selected from the group consisting of halogen, hydroxyl, amino, alkoxyl, alkyl, cyano, nitro, carboxyl, alkoxycarbonyl, aminocarbonyl which may have, at the amino moiety thereof, one or two substituents, aminosulfonyl which may have, at the amino moiety thereof, one  
20 or two substituents, aminoalkyl which may have, at the amino moiety thereof, one or two substituents and trifluoromethyl.

The substituents in Class (4) have the same meanings as described in Classes (1) to (3) of the description of  
25 the group  $Q^A$ .

In the present invention, preferred examples of  $Q^1$  in-

clude a cyclopentyl group which may have a substituent, cyclohexyl group which may have a substituent, cyclopentenyl group which may have a substituent, cyclohexenyl group which may have a substituent, phenyl group which may have a substituent, pyrrolidinyl group which may have a substituent, piperidinyl group which may have a substituent, imidazolyl group which may have a substituent, thiazolyl group which may have a substituent, thiadiazolyl group which may have a substituent, pyridyl group which may have a substituent, pyrimidinyl group which may have a substituent, pyridazinyl group which may have a substituent, thiazolindinyl group which may have a substituent, morpholinyl group which may have a substituent, piperazinyl group which may have a substituent, thiomorpholinyl group which may have a substituent, pyrrolyl group which may have a substituent, thienyl group which may have a substituent, furanyl group which may have a substituent, tetrahydropyrimidinyl group which may have a substituent, tetrahydrofuranyl group which may have a substituent, tetrahydrothienyl group which may have a substituent, sulforanyl group which may have a substituent, imidazolinyl group which may have a substituent, thiazolinyl group which may have a substituent, oxazolyl group which may have a substituent, oxadiazinyl group which may have a substituent, triazinyl group which may have a substituent, tetrazinyl group which may have a substituent, pyrazinyl group which may have a substituent, pyrazolyl

group which may have a substituent, pyrazolinyl group which  
may have a substituent, pyrazolidinyl group which may have  
a substituent, thienopyridyl group which may have a sub-  
stituent, tetrahydrothienopyridyl group which may have a  
5 substituent, thiazolopyridyl group which may have a sub-  
stituent, tetrahydrothiazolopyridyl group which may have a  
substituent, pyranothiazolyl group which may have a sub-  
stituent, dihydropyranothiazolyl group which may have a  
substituent, thiazolopyridadiny group which may have a sub-  
10 stituent, tetrahydrothiazolopyridadiny group which may  
have a substituent, furopyridyl group which may have a sub-  
stituent, tetrahydrofuropyridyl group which may have a sub-  
stituent, oxazolopyridyl group which may have a substitu-  
ent, and tetrahydrooxazolopyridyl group which may have a  
15 substituent.

Examples of the substituent include a hydroxyl group,  
an alkyl group, a hydroxyalkyl group, a halogen atom, a  
cyano group, a nitro group, a carboxyl group, an alkoxycar-  
bonyl group, a formyl group, an alkylsulfonyl group, an  
20 amino group which may have one or two substituents, an ami-  
nosulfonyl group which may have, at the amino moiety  
thereof, one or two substituents, an aminoalkyl group which  
may have, at the amino moiety thereof, one or two substitu-  
ents, an oxygen atom, a trifluoromethyl group, a saturated  
25 or unsaturated 5- or 6-membered cyclic hydrocarbon group  
which may have 1 to 3 substituents selected from the group



consisting of a halogen atom, a hydroxyl group, an amino group, an alkoxyl group, an alkyl group, a cyano group, a nitro group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents, an aminosulfonyl group which may have, at the amino moiety thereof, one or two substituents, an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents and a trifluoromethyl group, and a saturated or unsaturated 5- or 6-membered heterocyclic group which may have 1 to 3 substituents selected from the group consisting of a halogen atom, a hydroxyl group, an amino group, an alkoxyl group, an alkyl group, a cyano group, a nitro group, a carboxyl group, an alkoxycarbonyl group, an aminocarbonyl group which may have, at the amino moiety thereof, one or two substituents, an aminosulfonyl group which may have, at the amino moiety thereof, one or two substituents, an aminoalkyl group which may have, at the amino moiety thereof, one or two substituents and a trifluoromethyl group

<About  $Q^2$ >

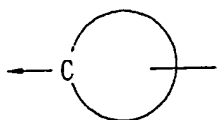
$Q^2$  represents a single bond, an oxygen atom, a sulfur atom, a linear or branched  $C_{1-6}$  alkylene group, a linear or branched  $C_{2-6}$  alkenylene group, a linear or branched  $C_{2-6}$  alkynylene group,  
a group  $-N(R^1)-CO-$   
(wherein,  $R^1$  represents a hydrogen atom or an alkyl group),

a group- $N(R^2)-(CH_2)_m-$

(wherein,  $R^2$  represents a hydrogen atom or an alkyl group

and  $m$  stands for an integer of 0 to 6), or

a group:



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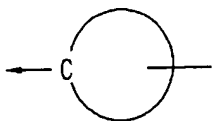
(which represents a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent, a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent or  
10 a divalent, saturated or unsaturated dicyclic fused ring group which may have a substituent and  $\leftarrow C$  means the bonding of the carbon atom of this group to  $Q^1$ ),

In  $Q^2$ , examples of the linear or branched  $C_{1-6}$  alkylene group include methylene, ethylene, trimethylene, propylene,  
15 tetramethylene, butylene, pentamethylene and hexamethylene.

Examples of the linear or branched  $C_{2-6}$  alkenylene group include vinylene, propenylene, butenylene and pentenylene. There is no particular limitation on the position of the double bond.

20 Examples of the linear or branched  $C_{2-6}$  alkynylene group include propynylene, butynylene, pentynylene and hexynylene.

The group of the following formula:

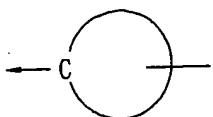


means a divalent, saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent a divalent, saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent or a divalent, saturated or unsaturated dicyclic fused ring group which may have a substituent and  $\leftarrow C$  means the bonding of the carbon atom of this group to  $Q^1$ . Examples of the group include divalent groups derived from thiophene, furan, pyran, pyrrole, pyrrolidine, pyrroline, imidazole, imidazoline, imidazolidine, pyrazole, pyrazolidine, thiazole, oxazole, oxathiolane, benzene, pyridine, piperidine, piperazine, morpholine, thiomorpholine, pyrazine, pyrimidine, pyridazine, triazine, tetrazine, thiadiazine, dithiazine, cyclopentane, cyclopentene, cyclopentadiene, cyclohexane, cyclohexene and they may have a substituent. Examples of the substituent are similar to those exemplified in Class (4).

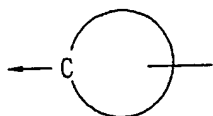
The alkyl group in  $R^1$  or  $R^2$  of the group  $-N(R^1)-CO-$  or  $-N(R^2)-(CH_2)_m-$  means a linear, branched or cyclic  $C_{1-6}$  alkyl group. Examples include methyl, ethyl, isopropyl and cyclopropyl. As the group  $-N(R^1)-CO-$ , a group  $\leftarrow N(R^1)-CO-$  (wherein  $\leftarrow$  means the bonding of the nitrogen atom of this group to  $Q^1$ ) is preferred, while as the group  $-N(R^2)-(CH_2)_m-$

, a group  $\leftarrow N(R^2)-(CH_2)_m-$  (wherein  $\leftarrow$  means the bonding of the nitrogen atom of this group to  $Q^1$ ) is preferred.

In the present invention,  $Q^2$  preferably represents a single bond, a carbonyl group or a group of the following  
5 formula:



and as the group represented by the following formula:



divalent groups derived from benzene, pyrimidine, tetrahy-  
10 dropyrimidine, pyrazine, pyridazine, triazine, tetrazine, imidazole, imidazoline, thiazole, thiazoline, furan, thiophene, pyrrole, oxazole, oxazoline, thiadiazole, cyclopentane, cyclopentene, cyclohexane or cyclohexene.

<About  $Q^3$ >

15 In  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^{10}$  and  $R^{11}$  as the substituents in  $Q^3$ , the alkyl, alkoxyl, alkoxyalkyl, hydroxyalkyl, hydroxyalkyloxy, hydroxyalkylcarbonyl, hydroxyalkylsulfonyl, formylalkyl, formylalkylcarbonyl, formylalkylsulfonyl, alkylcarbonyl, alkylsulfonyl, alkylcarbonylalkyl, alkylsulfonylalkyl, carboxyalkyl, carboxyalkylcarbonyl, carboxyalkylsulfonyl, carboxyalkylcarbonylalkyl, carboxyalkylsulfonylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycar-

20

bonylalkylcarbonyl, alkoxycarbonylalkylsulfonyl, amino  
 which may have 1 to 2 substituents, aminoalkyl which may  
 have, at the amino moiety thereof, one or two substituents,  
 aminoalkyloxy which may have, at the amino moiety thereof,  
 5 one or two substituents, aminoalkylcarbonyl which may have,  
 at the amino moiety thereof, one or two substituents, ami-  
 noalkylcarbonyloxy which may have, at the amino moiety  
 thereof, one or two substituents, aminocarbonyl which may  
 have, at the amino moiety thereof, one or two substituents,  
 10 aminocarbonylalkyl which may have, at the amino moiety  
 thereof, one or two substituents, and aminocarbonylalkyloxy  
 which may have, at the amino moiety thereof, one or two  
 substituents have the same meanings as described above in  
 $R^{15}$  of the description of the group  $Q^A$ .

15 The "alkoxyalkyloxy group" means a group formed of the  
 above-described alkoxyalkyl group and an oxygen atom and  
 examples include methoxymethyloxy, methoxyethyloxy and eth-  
 oxymethyloxy.

20 The "carboxyalkyloxy group" means a group formed of  
 the above-described carboxyalkyl group and an oxygen atom  
 and examples include carboxymethoxyl and carboxyethoxyl.

The "carboxyalkyloxy group" means a group formed of  
 the above-described carboxylalkyl group and an oxygen atom  
 and examples include carboxymethoxyl and carboxyethoxyl.

25 The "alkoxycarbonylalkyloxy group" means a group  
 formed of the above-described alkoxycarbonylalkyl group and

an oxygen atom and examples include methoxycarbonylethyl and ethoxycarbonylethyl.

The "alkylsulfonylaminocarbonylalkyl group which may have, at the amino moiety thereof, one substituent" means a group formed of the above-described alkylsulfonyl group, an imino group which may have one substituent and a carbonyl group and examples include methylsulfonylaminocarbonylmethyl.

The "arylsulfonylaminocarbonylalkyl group which may have, at the amino moiety thereof, one substituent" means a group formed of an aryl group, a sulfonyl group, an imino group which may have one substituent and a carbonyl group and examples include phenylsulfonylaminocarbonylmethyl.

The "aminosulfonylalkyl group which may have, at the amino moiety thereof, one or two substituents" means a group formed of an amino group which may have one or two substituents, a sulfonyl group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group and examples include aminosulfonylmethyl.

The "cyanoalkyl group" means a group formed of a cyano group and a linear, branched or cyclic C<sub>1-6</sub> alkylene group.

The "alkylcarbonyloxyalkyl group" means a group formed of the above-described alkylcarbonyl group, an oxygen atom and a linear, branched or cyclic C<sub>1-6</sub> alkylene group and examples include methylcarbonyloxyethyl.

The "alkoxyalkylaminocarbonylalkyl group which may

have, at the amino moiety thereof, one substituent" means a group formed of the above-described alkoxyalkyl group, an imino group which may have one substituent and a carbonyl group and examples include ethoxymethylaminocarbonylmethyl.

5           In the group  $A^1-B^1-$ ,  $A^1$  represents a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent. Here, examples of the saturated or unsaturated 5- or 6-  
10          membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has various structural isomers as the cyclopentenyl group, they are all embraced in it.

15           The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thi-  
20          enyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tet-  
25          razolyl, triazolyl and triazinyl. Where the group has plural structural isomers as the pyranyl group, they are all

embraced in it.

B<sup>1</sup> represents a single bond, carbonyl group, alkylene group, carbonylalkyl group, a group -O- C<sub>1-6</sub> alkylene, a group -COO- C<sub>1-6</sub> alkylene, a group -NHCO- or a group -NHCO- C<sub>1-6</sub> alkylene.

Examples of the group A<sup>1</sup>-B<sup>1</sup>- include the following groups:

a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent,

a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and a carbonyl group, and

a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and an alkylene group.

Each of R<sup>3</sup> and R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup>, and R<sup>10</sup> and R<sup>11</sup> are coupled together with a carbon atom which constitutes the ring and represents a saturated or unsaturated 5- to 7-membered cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent. Here, examples of the saturated or unsaturated 5- or 7-membered cyclic hydrocarbon group include cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl and phenyl. When the group has various structural isomers as the cyclopentenyl, they are all embraced in it.



The saturated or unsaturated 5- or 6-membered heterocyclic group is a cyclic group having at least one hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has plural structural isomers as the pyranyl, they are all embraced in it.

In  $R^9$  or  $R^{12}$  as the substituent in  $Q^3$ , the alkyl, hydroxyalkyl, alkoxyl, hydroxyalkylcarbonyl, hydroxyalkylsulfonyl, alkoxyalkyl, alkoxyalkylcarbonyl, alkoxyalkylsulfonyl, formylalkyl, formylalkylcarbonyl, formylalkylsulfonyl, alkylcarbonyl, alkylsulfonyl, alkylcarbonylalkyl, alkylsulfonylalkyl, carboxyalkylcarbonyl, carboxyalkylsulfonyl, carboxyalkylcarbonylalkyl, carboxyalkylsulfonylalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, alkoxy carbonylalkylcarbonyl, alkoxy carbonylalkylsulfonyl, amino which may have 1 to 2 substituents, aminoalkyl which may have, at the amino moiety thereof, aminoalkyloxy which may have, at the amino moiety thereof, aminoalkylcarbonyl which may have, at the amino moiety thereof, one or two substituents, aminoalky-

loxycarbonyl which may have, at the amino moiety thereof, 1  
or 2 substituents, aminocarbonyl which may have, at the  
amino moiety thereof, one or two substituents, aminocar-  
bonylalkyl which may have, at the amino moiety thereof, one  
5 or two substituents, and aminocarbonyloxyalkyl which may  
have, at the amino moiety thereof, one or two substituents  
have the same meanings as described in Q<sup>A</sup>.

In the group A<sup>2</sup>-B<sup>2</sup>-, A<sup>2</sup> represents a saturated or un-  
saturated 5- or 6-membered cyclic hydrocarbon group which  
10 may have a substituent or a saturated or unsaturated 5- or  
6-membered heterocyclic group which may have a substituent.  
Here, examples of the saturated or unsaturated 5- or 6-  
membered cyclic hydrocarbon group include cyclopentyl, cy-  
clopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl,  
15 cyclohexadienyl and phenyl. When the group has plural  
structural isomers as the cyclopentenyl, they are all em-  
braced in it.

The saturated or unsaturated 5- or 6-membered hetero-  
cyclic group is a cyclic group having at least one hetero  
20 atom. Examples of the hetero atom include oxygen, nitrogen  
and sulfur. Examples of the saturated or unsaturated 5- or  
6-membered heterocyclic group include furyl, pyrrolyl, thi-  
enyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl,  
oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadi-  
25 azolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrroli-  
diny, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl,

morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, tetrazolyl, triazolyl and triazinyl. Where the group has plural structural isomers as the pyranyl, they are all embraced in it.

5             $B^2$  represents a single bond, carbonyl group, alkylene group, carbonylalkyl group, a group  $-O-$   $C_{1-6}$  alkylene, a group  $-COO-$   $C_{1-6}$  alkylene, a group  $-NHCO-$  or a group  $-NHCO-$   $C_{1-6}$  alkylene.

10           Examples of the group  $A^2-B^2-$  include the following groups:

          a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent,

          a group formed of a saturated or unsaturated 5- or 6-membered cyclic hydrocarbon group which may have a substituent and a carbonyl group, and

15

          a group formed of a saturated or unsaturated 5- or 6-membered heterocyclic group which may have a substituent and an alkylene group.

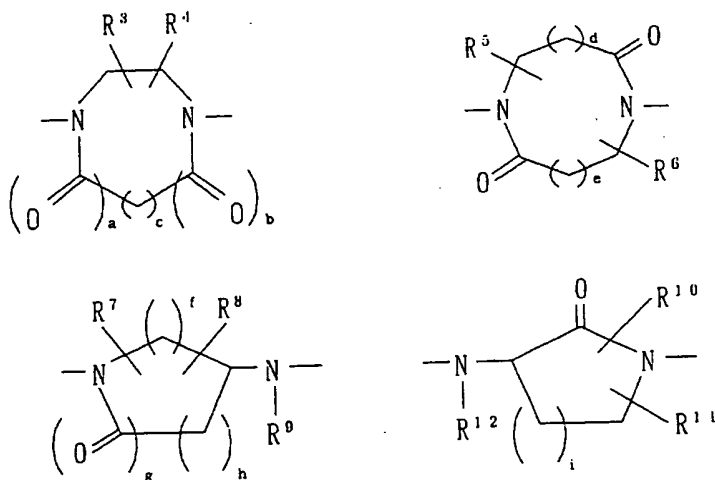
20            $R^9$  and  $R^7$ ,  $R^9$  and  $R^8$ ,  $R^{12}$  and  $R^{10}$ , and  $R^{12}$  and  $R^{11}$  are each coupled together with the carbon atom which constitutes the ring and the nitrogen atom to which  $R^9$  or  $R^{12}$  has been bonded and represent a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent. Here, the saturated or unsaturated 5- to 7-membered heterocyclic group is a cyclic group which has at least one ni-

25

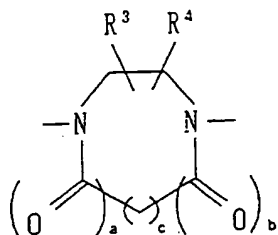
trogen atom and may have a hetero atom. Examples of the hetero atom include oxygen, nitrogen and sulfur. Examples of the saturated or unsaturated 5- or 6-membered heterocyclic group include furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, pyrazolinyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, oxatriazolyl, thiadiazolyl, furazanyl, pyranyl, pyridyl, pyridazinyl, pyrrolidinyl, piperazinyl, piperidinyl, oxazinyl, oxadiazinyl, morpholinyl, thiazinyl, thiadiazinyl, thiomorpholinyl, triazolyl and triazinyl.

Where the group has plural structural isomers as the pyranyl, they are all embraced in it.

In the present invention,  $Q^3$  represents a group of the following formula:



(wherein  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ ,  $a$ ,  $b$ ,  $c$ ,  $d$ ,  $e$ ,  $f$ ,  $g$ ,  $h$  and  $i$  have the same meanings as described above). Preferred as  $Q^3$  is a group of the following formula:



(wherein R<sup>3</sup>, R<sup>4</sup>, a, b and c have the same meanings as described above), of which the group wherein:

R<sup>3</sup> and R<sup>4</sup> each independently represents

- 5 a hydrogen atom,
- a hydroxyalkyl group,
- a cyanoalkyl group,
- a carboxyl group,
- a carboxyalkyl group,
- 10 an alkoxycarbonyl group,
- an alkoxycarbonylalkyl group,
- a carboxyalkylaminocarbonyl group,
- a carboxyalkylaminocarbonylalkyl group,
- an alkoxycarbonylalkylaminocarbonyl group,
- 15 an alkoxycarbonylalkylaminocarbonylamino group,
- a carbamoyl group,
- a monoalkylcarbamoyl group,
- a dialkylcarbamoyl group,
- a carbamoylalkyl group,
- 20 a monoalkylcarbamoylalkyl group,
- a dialkylcarbamoylalkyl group,
- a morpholinylcarbonyl group

a morpholinylcarbonylalkyl group,  
 a tetrazolylaminocarbonyl group,  
 a tetrazolylaminocarbonylalkyl group,  
 a tetrazolylalkyl group,  
 5 a tetrazolylalkylaminocarbonyl group, or  
 a tetrazolylalkylaminocarbonylalkyl group,  
 an aminoalkyl group which may have, at the amino moiety  
 thereof, one or two substituents,  
 an alkylaminosulfonylalkyl group,  
 10 an oxopyrrolidinylalkyl group,  
 oxopiperidinylalkyl group, or  
 oxooxazolidinylalkyl group, and  
 a stands for 0, b stands for 0 and c stands for 2 is  
 more preferred.

15 <About  $T^1$ >

$T^1$  represents a carbonyl group,

a group  $-CH(R^{13})-$

(in which  $R^{13}$  represents a hydrogen atom, an alkyl group, a  
 hydroxyalkyl group, an alkoxyalkyl group, a carboxyalkyl  
 20 group, an alkoxycarbonylalkyl group, an aryl group, an  
 aralkyl group, a heteroaryl group, a heteroarylalkyl group  
 or an aminoalkyl group which may have, at the amino moiety  
 thereof, a substituent), or

a group  $-C(=NOR^{14})-$  or  $-C(=N-NHR^{14'})-$

25 (in which  $R^{14}$  and  $R^{14'}$  each independently represents a hydro-  
 gen atom, an alkyl group, a carboxyalkyl group, an alkoxy-

carbonyl group, an aryl group, an aralkyl group, a hetero-aryl group, a heteroarylalkyl group or an aminoalkyl group which may have, at the amino moiety thereof, a substituent).

5        Here, in  $R^{13}$  and  $R^{14}$ , the alkyl, carboxyalkyl, alkoxy-carbonyl, aryl, aralkyl, heteroaryl, heteroarylalkyl and aminoalkyl which may have, at the amino moiety thereof, a substituent have the same meanings as described in  $Q^A$ . In the present invention, a carbonyl group is preferred as  $T^1$ .

10        The sulfonyl derivative of the present invention has optical isomers or stereoisomers based on an asymmetric carbon atom. These optical isomers and stereoisomers and mixtures thereof are all embraced in the present invention.

15        Although there is no particular limitation imposed on the salt of the sulfonyl derivative according to the present invention insofar as it is a pharmaceutically acceptable salt. Specific examples include salts of a mineral acid such as hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate and sulfate, salts of an organic sul-  
20        fonic acid such as benzoate, methanesulfonate, 2-hydroxyethanesulfonate and p-toluenesulfonate and salts of an organic carboxylic acid such as acetate, propanoate, oxalate, malonate, succinate, glutarate, adipate, tartrate, maleate, malate and mandelate. There is no particular  
25        limitation imposed on the solvate insofar as it is pharmaceutically acceptable. Specific examples include hydrates

and ethanolates.

The following are the preferred compounds as the sulfonyl derivative of the present invention.

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[2-[(N,N-  
5 dimethyl)amino]ethyl]-4-methylthiazol-2-  
yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[2-[(N,N-  
dimethyl)amino]ethyl]thiazol-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[3-[(N,N-  
10 dimethyl)amino]propyl]-4-methylthiazol-2-  
yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[3-[(N,N-  
dimethyl)amino]propyl]thiazol-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[2-[(N,N-  
15 dimethyl)amino]ethyl]-4-methylthiazol-2-  
yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[2-[(N,N-  
dimethyl)amino]ethyl]thiazol-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[3-[(N,N-  
20 dimethyl)amino]propyl]-4-methylthiazol-2-  
yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[3-[(N,N-  
dimethyl)amino]propyl]thiazol-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[2-[(N,N-  
25 dimethyl)amino]ethyl]-4-methylthiazol-2-  
yl]carbonyl]piperazine



1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[2-[(N,N-dimethyl)amino]ethyl]thiazol-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[3-[(N,N-dimethyl)amino]propyl]-4-methylthiazol-2-

5 yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[3-[(N,N-dimethyl)amino]propyl]thiazol-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[(1-methylpiperidin)-4-yl]thiazol-2-yl]carbonyl]piperazine

10 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[(1-methylpiperidin)-3-yl]thiazol-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[(1-methylpiperidin)-2-yl]thiazol-2-yl]carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methylpiperidin)-4-yl]thiazol-2-yl]carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methylpiperidin)-3-yl]thiazol-2-yl]carbonyl]piperazine

20 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methylpiperidin)-2-yl]thiazol-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

25 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(1-methylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

1-[[5-(1-Carbamoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

5 1-[[5-(1-Acetoimidoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-(pyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

10 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-(1-methylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

15 1-[[5-(1-Carbamoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

1-[[5-(1-Acetoimidoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

20 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[(1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[(1-methyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

25 1-[[5-[(1-Carbamoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[[5-[(1-Acetoimidoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

1-[[5-[(1-Carbamoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

1-[[5-[(1-Acetoimidoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine

4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-3-yl)thiazol-2-yl]carbonyl]piperazine

3-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)thiazol-2-yl]carbonyl]piperazine

2-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-

yl]carbonyl]thiazol-5-yl]pyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[(1-methylpiperidin)-4-yl]thiazol-2-yl]carbonyl]piperazine

5 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[(1-methylpiperidin)-3-yl]thiazol-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[(1-methylpiperidin)-2-yl]thiazol-2-yl]carbonyl]piperazine

10 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methylpiperidin)-4-yl]thiazol-2-yl]carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methylpiperidin)-3-yl]thiazol-2-yl]carbonyl]piperazine

15 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methylpiperidin)-2-yl]thiazol-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

20 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(1-methylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

1-[[5-(1-Carbamoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

1-[[5-(1-Acetoimidoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

25 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-(pyrrolidin-3-yl)thiazol-2-

yl]carbonyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-(1-methylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

5 1-[[5-(1-Carbamoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

1-[[5-(1-Acetoimidoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

10 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[(1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[(1-methyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

15 1-[[5-[(1-Carbamoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

1-[[5-[(1-Acetoimidoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

20 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

25 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methyl-1,2,5,6-

tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine  
 1-[[5-[(1-carbamoyl-1,2,5,6-tetrahydropyridin)-4-  
 yl]thiazol-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-  
 2-[(N-methyl)carbamoyl]piperazine  
 5 1-[[5-[(1-Acetoimidoyl-1,2,5,6-tetrahydropyridin)-4-  
 yl]thiazol-2-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-  
 2-[(N-methyl)carbamoyl]piperazine  
 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-  
 yl)thiazol-2-yl]carbonyl]piperazine  
 10 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-  
 yl]carbonyl]thiazol-5-yl]pyridine N-oxide  
 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-3-  
 yl)thiazol-2-yl]carbonyl]piperazine  
 3-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-  
 15 yl]carbonyl]thiazol-5-yl]pyridine N-oxide  
 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-2-  
 yl)thiazol-2-yl]carbonyl]piperazine  
 2-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-  
 yl]carbonyl]thiazol-5-yl]pyridine N-oxide  
 20 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[(1-  
 methylpiperidin)-4-yl]thiazol-2-yl]carbonyl]piperazine  
 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[(1-  
 methylpiperidin)-3-yl]thiazol-2-yl]carbonyl]piperazine  
 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[(1-  
 25 methylpiperidin)-2-yl]thiazol-2-yl]carbonyl]piperazine  
 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-

methy1)carbamoyl]-1-[[5-[(1-methylpiperidin)-4-yl]thiazol-  
2-yl]carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-  
methy1)carbamoyl]-1-[[5-[(1-methylpiperidin)-3-yl]thiazol-  
5 2-yl]carbonyl]piperazine

4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-  
methy1)carbamoyl]-1-[[5-[(1-methylpiperidin)-2-yl]thiazol-  
2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-  
10 (pyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(1-  
methy1pyrrolidin-3-yl)thiazol-2-yl]carbonyl]piperazine

1-[[5-(1-Carbamoylpyrrolidin-3-yl)thiazol-2-  
yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-  
15 yl)sulfonyl]piperazine

1-[[5-(1-Acetoimidoylpyrrolidin-3-yl)thiazol-2-  
yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-  
yl)sulfonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-  
20 methy1)carbamoyl]-1-[[5-(pyrrolidin-3-yl)thiazol-2-  
yl]carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-  
methy1)carbamoyl]-1-[[5-(1-methylpyrrolidin-3-yl)thiazol-2-  
yl]carbonyl]piperazine

25 1-[[5-(1-Carbamoylpyrrolidin-3-yl)thiazol-2-  
yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-

[(N-methyl)carbamoyl]piperazine

1-[[5-(1-Acetoimidoylpyrrolidin-3-yl)thiazol-2-yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

5 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[(1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[(1-methyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

10

1-[[5-[(1-Carbamoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

1-[[5-[(1-Acetoimidoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

15

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]-1-[[5-[(1-methyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]piperazine

20

1-[[5-[(1-Carbamoyl-1,2,5,6-tetrahydropyridin)-4-yl]thiazol-2-yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

25

1-[[5-[(1-Acetoimidoyl-1,2,5,6-tetrahydropyridin)-4-



yl]thiazol-2-yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methyl)carbamoyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)thiazol-2-yl]carbonyl]piperazine

5 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(pyridin-3-yl)thiazol-2-yl]carbonyl]piperazine

10 3-[2-[[4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)thiazol-2-yl]carbonyl]piperazine

15 2-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thiazol-5-yl]pyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[1,2-dihydro-2-oxo-6-(pyridin-4-yl)pyridin-3-yl]carbonyl]piperazine

20 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[1,2-dihydro-2-oxo-6-(pyridin-4-yl)pyridin-3-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[1,2-dihydro-2-oxo-6-(pyridin-4-yl)pyridin-3-yl]carbonyl]piperazine

25 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)-pyridazin-3-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)-pyridazin-3-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)-pyridazin-3-yl]carbonyl]piperazine

5 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

10 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2,5-dihydro-5-oxo-6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

15 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

20 4-[3-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2-dihydro-2-oxopyridin-6-yl]pyridine N-oxide

4-[3-[[4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2-dihydro-2-oxopyridin-6-yl]pyridine N-oxide

25 4-[3-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2-dihydro-2-oxopyridin-6-yl]pyridine N-oxide

4-[6-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-

yl]carbonyl]pyridazin-3-yl]pyridine N-oxide

4-[6-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyridazin-3-yl]pyridine N-oxide

5 4-[6-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyridazin-3-yl]pyridine N-oxide

4-[6-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2,4-triazin-3-yl]pyridine N-oxide

10 4-[6-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2,4-triazin-3-yl]pyridine N-oxide

4-[6-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2,4-triazin-3-yl]pyridine N-oxide

15 4-[3-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-2,5-dihydro-5-oxo-1,2,4-triazin-6-yl]pyridine N-oxide

4-[3-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2,4-triazin-6-yl]pyridine N-oxide

20 4-[3-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2,4-triazin-6-yl]pyridine N-oxide

4-[3-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-1,2,4-triazin-6-yl]pyridine N-oxide

25 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(2-

methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

5 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(2-hydroxymethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(2-hydroxymethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

10 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2-hydroxymethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(2,6-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

15 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(2,6-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2,6-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

20 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(2,3-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(2,3-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2,3-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

25 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(3-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(3-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(3-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

5 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(3-fluoropyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(3-fluoropyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

10 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2-fluoropyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(2,5-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(2,5-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

15 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(2,5-dimethylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

20 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

25 4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-hydroxymethylpyridine N-oxide

4-[2-[[4-[(6-Chlorobenzo[b]thien-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-hydroxymethylpyridine N-oxide

4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-hydroxymethylpyridine N-oxide

5 4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,6-dimethylpyridine N-oxide

4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,6-dimethylpyridine N-oxide

10 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,6-dimethylpyridine N-oxide

4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,3-dimethylpyridine N-oxide

15 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,3-dimethylpyridine N-oxide

4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,3-dimethylpyridine N-oxide

20 4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-3-methylpyridine N-oxide

4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-3-methylpyridine N-oxide

25 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-3-methylpyridine N-oxide

4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-

yl]carbonyl]pyrimidin-5-yl]-3-fluoropyridine N-oxide

4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-3-fluoropyridine N-oxide

5 4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-fluoropyridine N-oxide

4-[2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,5-dimethylpyridine N-oxide

10 4-[2-[[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,5-dimethylpyridine N-oxide

4-[2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2,5-dimethylpyridine N-oxide

15 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)-3,4,5,6-tetrahydropyrimidin-5-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)-3,4,5,6-tetrahydropyrimidin-5-yl]carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)-3,4,5,6-tetrahydropyrimidin-5-yl]carbonyl]piperazine

20 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5,6-dihydro-2-(pyridin-4-yl)oxazin-5-yl]carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5,6-dihydro-2-(pyridin-4-yl)oxazin-5-yl]carbonyl]piperazine

25 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5,6-dihydro-2-(pyridin-4-yl)oxazin-5-yl]carbonyl]piperazine

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-8-

[4-(pyridin-4-yl)benzoyl]-3,8-diazabicyclo[3.2.1]octane

4-[4-[[[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan]-8-yl]carbonyl]phenyl]pyridine N-oxide

5 3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-8-[4-(pyridin-4-yl)benzoyl]-3,8-diazabicyclo[3.2.1]octane

4-[4-[[[3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan]-8-yl]carbonyl]phenyl]pyridine N-oxide

10 3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-8-[4-(pyridin-4-yl)benzoyl]-3,8-diazabicyclo[3.2.1]octane

4-[4-[[[3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan]-8-yl]carbonyl]phenyl]pyridine N-oxide

15 3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-8-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[2-[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

20 3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-8-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

25 4-[5-[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrimidin-2-yl]pyridine N-oxide



3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-8-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

5 4-[5-[3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-8-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

10 4-[2-[3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

15 3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-8-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[5-[3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

20 3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-8-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[2-[3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

25 3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-8-[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]-3,8-

diazabicyclo[3.2.1]octane

4-[5-[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrazin-2-yl]pyridine N-oxide

5 3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-8-[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[5-[3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrazin-2-yl]pyridine N-oxide

10

3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-8-[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[5-[3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyrazin-2-yl]pyridine N-oxide

15

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-8-[[6-(pyridin-4-yl)pyridazin-3-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

20

4-[6-[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyridazin-3-yl]pyridine N-oxide

3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-8-[[6-(pyridin-4-yl)pyridazin-3-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

25

4-[6-[3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-

3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyridazin-3-yl]pyridine N-oxide

3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-8-[[6-(pyridin-4-yl)pyridazin-3-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[6-[3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonylpyridazin-3-yl]pyridine N-oxide

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-8-[[6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[3-[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-8-[[3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[6-[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-8-[[6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[3-[3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-8-[[3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

5 4-[6-[3-[(5-Chloroindol-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-8-[[6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

10 4-[3-[3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

15 3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-8-[[3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]-3,8-diazabicyclo[3.2.1]octane

4-[6-[3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-6,7-dihydroxy-3,8-diazabicyclo[3.2.1]octan-8-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

20 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2-(pyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

25 2-[5-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

5 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-(pyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

2-[5-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

10 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[2-(pyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

15 2-[5-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrazin-2-yl]carbonyl]piperazine

20 2-[5-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrazin-2-yl]pyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrazin-2-yl]carbonyl]piperazine

2-[5-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrazin-2-yl]pyridine N-oxide

25 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrazin-2-yl]carbonyl]piperazine

2-[5-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrazin-2-yl]pyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)pyridazin-3-yl]carbonyl]piperazine

5        2-[6-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyridazin-3-yl]pyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)pyridazin-3-yl]carbonyl]piperazine

10       2-[6-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyridazin-3-yl]pyridine N-oxide

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)pyridazin-3-yl]carbonyl]piperazine

2-[6-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyridazin-3-yl]pyridine N-oxide

15       1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

2-[3-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

20       1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[3-(pyridin-2-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

2-[6-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

25       2-[3-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[3-(pyridin-2-yl)-  
1,2,4-triazin-6-yl]carbonyl]piperazine

2-[6-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-  
yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

5 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[6-(pyridin-  
2-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

2-[3-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-  
1-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

10 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[3-(pyridin-  
2-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

2-[6-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-  
1-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

15 1-[[5-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-2-  
yl]carbonyl]-4-[(6-chloronaphthalen-2-  
yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[2-[4-[(6-chloronaphthalen-2-  
yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine  
N-oxide

20 1-[[2-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-5-  
yl]carbonyl]-4-[(6-chloronaphthalen-2-  
yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[5-[4-[(6-chloronaphthalen-2-  
yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine  
N-oxide

25 1-[[5-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-2-  
yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[2-[4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

1-[[2-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-5-yl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[5-[4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

1-[[5-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-2-yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[2-[4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

1-[[2-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-5-yl]carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[5-[4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(6-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-methylpyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2-(6-methylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine



2-[5-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-methylpyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(6-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

5 2-[2-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-methylpyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-(6-methylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

10 2-[5-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-methylpyridine N-oxide

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(6-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-methylpyridine N-oxide

15 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[2-(6-methylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

2-[5-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-methylpyridine N-oxide

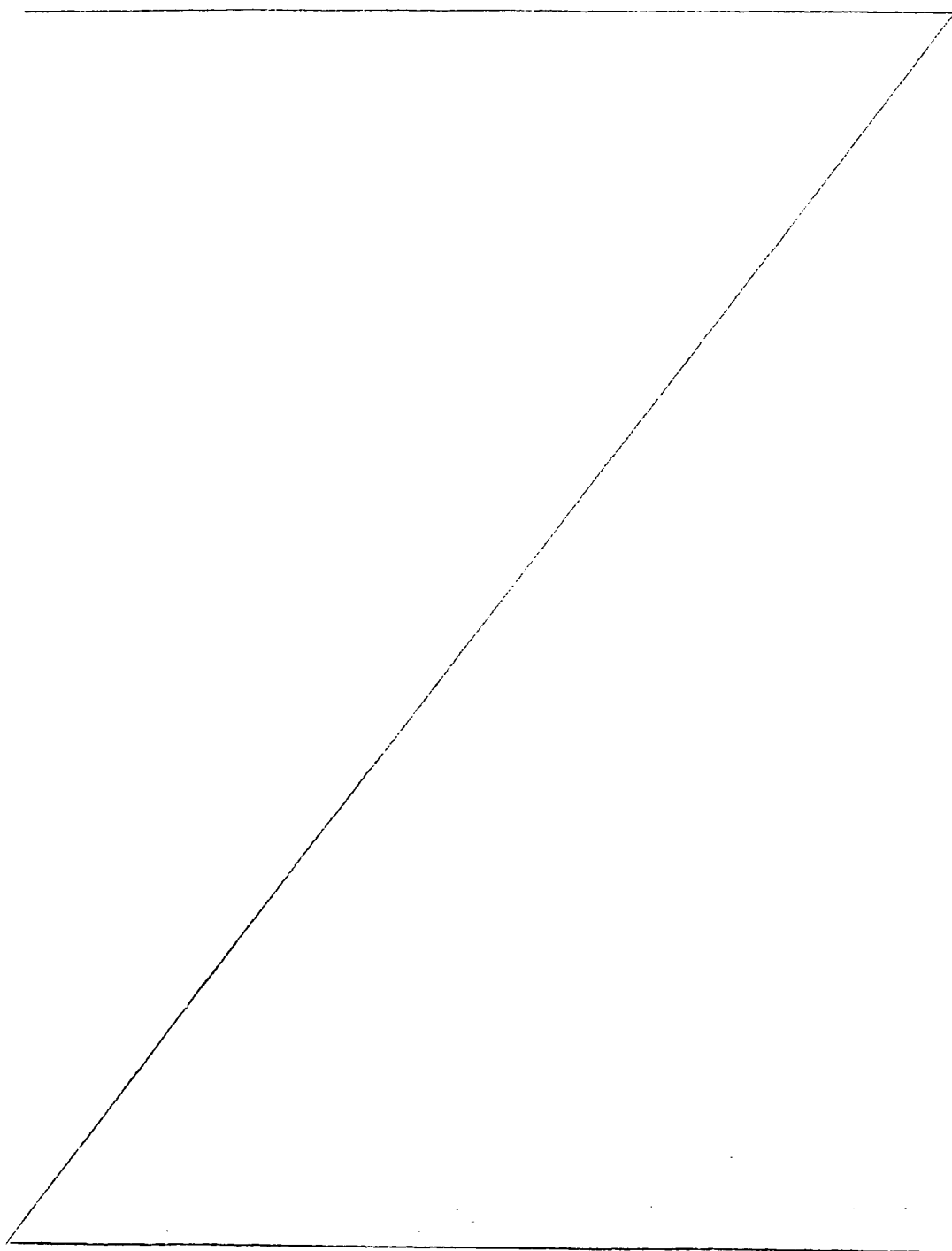
20 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[4-(4-methylpyridin-2-yl)phenyl]carbonyl]piperazine

2-[4-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-6-methylpyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(4-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

25 2-[2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-4-methylpyridine N-oxide

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2-(4-methylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine



2-[5-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-4-methylpyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-(4-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

5 2-[2-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-4-methylpyridine N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-(4-methylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

10 2-[5-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-4-methylpyridine N-oxide

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-(4-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-4-methylpyridine N-oxide

15 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[2-(4-methylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

2-[5-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-4-methylpyridine N-oxide

20 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-(hydroxymethyl)pyridine N-oxide

25 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[2-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-5-

yl]carbonyl]piperazine

2-[5-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-(hydroxymethyl)pyridine N-oxide

5 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[5-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-(hydroxymethyl)pyridine N-oxide

10

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[2-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-5-yl]carbonyl]piperazine

2-[5-[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-(hydroxymethyl)pyridine N-oxide

15

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[5-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-2-yl]carbonyl]piperazine

20

2-[2-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-(hydroxymethyl)pyridine N-oxide

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[[2-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-5-

25

yl]carbonyl]piperazine

2-[5-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-

1-yl]carbonylpyrimidin-2-yl]-6-(hydroxymethyl)pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(pyridin-2-yl)phenyl]carbonyl]piperazine

5 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(pyridin-2-yl)phenyl]carbonyl]piperazine

2-[4-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

10 2-[4-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

15 2-[2-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

2-[2-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

20 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(pyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(pyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

2-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

25 2-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrazin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(pyridin-2-yl)pyrazin-2-yl]carbonyl]piperazine

5 2-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrazin-2-yl]pyridine N-oxide

2-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrazin-2-yl]pyridine N-oxide

10 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)pyridazin-3-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)pyridazin-3-yl]carbonyl]piperazine

2-[6-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyridazin-3-yl]pyridine N-oxide

15 2-[6-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyridazin-3-yl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

20 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[6-(pyridin-2-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

2-[3-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

2-[3-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

25 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[3-(pyridin-2-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[3-(pyridin-2-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

2-[6-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

5 2-[6-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

1-[[4-[6-(Aminomethyl)pyridin-2-yl]phenyl]carbonyl]-4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazine

10 1-[[4-[6-(Aminomethyl)pyridin-2-yl]phenyl]carbonyl]-4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[4-[4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

2-(Aminomethyl)-6-[4-[4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

15 1-[[5-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-2-yl]carbonyl]-4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazine

20 1-[[5-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-2-yl]carbonyl]-4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[2-[4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

25 2-(Aminomethyl)-6-[2-[4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

1-[[2-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-5-yl]carbonyl]-4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazine

5 1-[[2-[6-(Aminomethyl)pyridin-2-yl]pyrimidin-5-yl]carbonyl]-4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-6-[5-[4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

10 2-(Aminomethyl)-6-[5-[4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(6-methylpyridin-2-yl)phenyl]carbonyl]piperazine

15 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(6-methylpyridin-2-yl)phenyl]carbonyl]piperazine

2-[4-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-6-methylpyridine N-oxide

20 2-[4-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-6-methylpyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(6-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(6-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine

25 2-[2-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-methylpyridine N-oxide



- 2-[2-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-methylpyridine N-oxide
- 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(6-methylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine
- 5 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(6-methylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine
- 2-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-methylpyridine N-oxide
- 2-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-methylpyridine N-oxide
- 10 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(4-methylpyridin-2-yl)phenyl]carbonyl]piperazine
- 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(4-methylpyridin-2-yl)phenyl]carbonyl]piperazine
- 15 2-[4-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-4-methylpyridine N-oxide
- 2-[4-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-4-methylpyridine N-oxide
- 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(4-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine
- 20 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(4-methylpyridin-2-yl)pyrimidin-2-yl]carbonyl]piperazine
- 2-[2-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-4-methylpyridine N-oxide
- 25 2-[2-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-4-methylpyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(4-dimethylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(4-dimethylpyridin-2-yl)pyrimidin-5-yl]carbonyl]piperazine

5 2-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-4-methylpyridine N-oxide

2-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-4-methylpyridine N-oxide

10 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-[6-(hydroxymethyl)pyridin-2-yl]phenyl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-[6-(hydroxymethyl)pyridin-2-yl]phenyl]carbonyl]piperazine

2-[4-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-6-(hydroxymethyl)pyridine N-oxide

15 2-[4-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-6-(hydroxymethyl)pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-2-yl]carbonyl]piperazine

20 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-2-yl]carbonyl]piperazine

2-[2-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-6-(hydroxymethyl)pyridine N-oxide

25

2-[2-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-

1-yl]carbonylpyrimidin-5-yl]-6-(hydroxymethyl)pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-5-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-[6-(hydroxymethyl)pyridin-2-yl]pyrimidin-5-yl]carbonyl]piperazine

2-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-(hydroxymethyl)pyridine N-oxide

2-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-6-(hydroxymethyl)pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(pyridin-4-yl)phenyl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(pyridin-4-yl)phenyl]carbonyl]piperazine

4-[4-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

4-[4-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

4-[2-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

4-[2-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

5 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(pyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

10 4-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

4-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]piperazine

15 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrazin-2-yl]carbonyl]piperazine

4-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrazin-2-yl]pyridine N-oxide

20 4-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrazin-2-yl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)pyridazin-3-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)pyridazin-3-yl]carbonyl]piperazine

25 4-[6-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyridazin-3-yl]pyridine N-oxide

4-[6-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyridazin-3-yl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

5 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)-1,2,4-triazin-3-yl]carbonyl]piperazine

4-[3-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

10 4-[3-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-6-yl]pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[3-(pyridin-4-yl)-1,2,4-triazin-6-yl]carbonyl]piperazine

15 4-[6-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

4-[6-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonyl-1,2,4-triazin-3-yl]pyridine N-oxide

20 1-[[4-[2-(Aminomethyl)pyridin-4-yl]phenyl]carbonyl]-4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazine

1-[[4-[2-(Aminomethyl)pyridin-4-yl]phenyl]carbonyl]-4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-4-[4-[4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

25 2-(Aminomethyl)-4-[4-[4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]pyridine N-oxide

1-[[5-[2-(Aminomethyl)pyridin-4-yl]pyrimidin-2-yl]carbonyl]-4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazine

5 1-[[5-[2-(Aminomethyl)pyridin-4-yl]pyrimidin-2-yl]carbonyl]-4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazine

2-(Aminomethyl)-4-[2-[4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

10 2-(Aminomethyl)-4-[2-[4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]pyridine N-oxide

15 1-[[2-[2-(Aminomethyl)pyridin-4-yl]pyrimidin-5-yl]carbonyl]-4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazine

1-[[2-[2-(Aminomethyl)pyridin-4-yl]pyrimidin-5-yl]carbonyl]-4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazine

20 2-(Aminomethyl)-4-[5-[4-[(5-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

2-(Aminomethyl)-4-[5-[4-[(6-chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]pyridine N-oxide

25 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(2-methylpyridin-4-yl)phenyl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-(2-methylpyridin-4-yl)phenyl]carbonyl]piperazine

4-[4-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-2-methylpyridine N-oxide

5 4-[4-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-2-methylpyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

10 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carbonyl]piperazine

4-[2-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-2-methylpyridine N-oxide

4-[2-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-2-methylpyridine N-oxide

15 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(2-methylpyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-(2-methylpyridin-4-yl)pyrimidin-5-yl]carbonyl]piperazine

20 4-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-2-methylpyridine N-oxide

4-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-2-methylpyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-[2-(hydroxymethyl)pyridin-4-yl]phenyl]carbonyl]piperazine

25 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[4-[2-(hydroxymethyl)pyridin-4-yl]phenyl]carbonyl]piperazine

4-[4-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-2-(hydroxymethyl)pyridine N-oxide

4-[4-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylphenyl]-2-(hydroxymethyl)pyridine N-oxide

5 1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-[2-(hydroxymethyl)pyridin-4-yl]pyrimidin-2-yl]carbonyl]piperazine

1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[5-[2-(hydroxymethyl)pyridin-4-yl]pyrimidin-2-yl]carbonyl]piperazine

4-[2-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-2-(hydroxymethyl)pyridine N-oxide

4-[2-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-5-yl]-2-(hydroxymethyl)pyridine N-oxide

1-[(5-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-[2-(hydroxymethyl)pyridin-4-yl]pyrimidin-5-yl]carbonyl]piperazine

20 1-[(6-Chlorobenzimidazol-2-yl)sulfonyl]-4-[[2-[2-(hydroxymethyl)pyridin-4-yl]pyrimidin-5-yl]carbonyl]piperazine

4-[5-[4-[(5-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-1-yl]carbonylpyrimidin-2-yl]-2-(hydroxymethyl)pyridine N-oxide

4-[5-[4-[(6-Chlorobenzimidazol-2-yl)sulfonyl]piperazin-



1-yl]carbonylpyrimidin-2-yl]-2-(hydroxymethyl)pyridine N-oxide

1-[(5-Chloroisoindolin-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

5 4-[4-[[4-[(5-Chloroisoindolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

1-[(5-Chloroisoindolin-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

10 4-[4-[[4-[(5-Chloroisoindolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

1-[(5-Chloro-1-isoindolinon-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

4-[4-[[4-[(5-Chloroisoindolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

15 1-[(5-Chloro-2-isoindolinon-2-yl)sulfonyl]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

4-[4-[[4-[(5-Chloro-2-isoindolinon-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

20 1-[(1,2,3,4-Tetrahydro-5-chloroisoquinolin-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

4-[4-[[4-[(1,2,3,4-Tetrahydro-5-chloroisoquinolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25 1-[(1,2,3,4-Tetrahydro-5-chloroisoquinolin-2-yl)]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

4-[4-[[4-[(1,2,3,4-Tetrahydro-5-chloroisoquinolin-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-  
methylpyridine N-oxide

1-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-4-[4-  
(pyridin-4-yl)benzoyl]piperazine

5 4-[4-[4-[(5-Chloro-3-hydroxyindol-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

1-[(5-Chloro-3-hydroxyindol-2-yl)]-4-[4-(2-  
methylpyridin-4-yl)benzoyl]piperazine

10 4-[4-[4-[(5-Chloro-3-hydroxyindol-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-  
methylpyridine N-oxide

1-[(5-Chloro-3-methoxyindol-2-yl)sulfonyl]-4-[4-  
(pyridin-4-yl)benzoyl]piperazine

15 4-[4-[4-[(5-Chloro-3-methoxyindol-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

1-[(5-Chloro-3-methoxyindol-2-yl)]-4-[4-(2-  
methylpyridin-4-yl)benzoyl]piperazine

20 4-[4-[4-[(5-Chloro-3-methoxyindol-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-  
methylpyridine N-oxide

1-[(3-Acetoxy-5-Chloroindol-2-yl)sulfonyl]-4-[4-  
(pyridin-4-yl)benzoyl]piperazine

4-[4-[4-[(3-Acetoxy-5-chloroindol-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

25 1-[(3-Acetoxy-5-chloroindol-2-yl)]-4-[4-(2-  
methylpyridin-4-yl)benzoyl]piperazine

4-[4-[[4-[(3-Acetoxy-5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

5 1-[(5-Chloro-3-hydroxymethylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

4-[4-[[4-[(5-Chloro-3-hydroxymethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

1-[(5-Chloro-3-hydroxymethylindol-2-yl)]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

10 4-[4-[[4-[(5-Chloro-3-hydroxymethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

1-[(5-Chloro-3-methoxymethylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

15 4-[4-[[4-[(5-Chloro-3-methoxymethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

1-[(5-Chloro-3-methoxymethylindol-2-yl)]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

20 4-[4-[[4-[(5-Chloro-3-methoxymethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

1-[(1-Acetyl-5-chloroindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

25 4-[4-[[4-[(1-Acetyl-5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

1-[(1-Acetyl-5-chloroindol-2-yl)]-4-[4-(2-methylpyridin-

4-yl)benzoyl]piperazine

4-[4-[[4-[(1-Acetyl-5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

5 1-[(5-Chloro-1-formylindol-2-yl)sulfonyl]-4-[4-(pyridin-4-yl)benzoyl]piperazine

4-[4-[[4-[(5-Chloro-1-formylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

10 1-[(5-Chloro-1-formylindol-2-yl)]-4-[4-(2-methylpyridin-4-yl)benzoyl]piperazine

4-[4-[[4-[(5-Chloro-1-formylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]phenyl]-2-methylpyridine N-oxide

15 1-[(5-Chloroisoindolin-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloroisoindolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

1-[(5-Chloroisoindolin-2-yl)sulfonyl]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

20 4-[2-[[4-[(5-Chloroisoindolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

1-[(5-Chloro-1-isoindolinon-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

25 4-[2-[[4-[(5-Chloroisoindolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

1-[(5-Chloro-2-isoindolinon-2-yl)sulfonyl]-4-[[5-(2-

methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-2-isoindolinon-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

5 1-[(1,2,3,4-Tetrahydro-5-chloroisoquinolin-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(1,2,3,4-Tetrahydro-5-chloroisoquinolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

10

1-[(1,2,3,4-Tetrahydro-5-chloroisoquinolin-2-yl)]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(1,2,3,4-Tetrahydro-5-chloroisoquinolin-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

15

1-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

20

1-[(5-Chloro-3-hydroxyindol-2-yl)]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

25

1-[(5-Chloro-3-methoxyindol-2-yl)sulfonyl]-4-[[5-

(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-3-methoxyindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

5 1-[(5-Chloro-3-methoxyindol-2-yl)]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-3-methoxyindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

10 1-[(3-Acetoxy-5-chloroindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(3-Acetoxy-5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

15 1-[(3-Acetoxy-5-chloroindol-2-yl)]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(3-Acetoxy-5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

20 1-[(5-Chloro-3-hydroxymethylindol-2-yl)sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-3-hydroxymethylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

25 1-[(5-Chloro-3-hydroxymethylindol-2-yl)]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-3-hydroxymethylindol-2-yl) sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

1-[(5-Chloro-3-methoxymethylindol-2-yl) sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-3-methoxymethylindol-2-yl) sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

1-[(5-Chloro-3-methoxymethylindol-2-yl)]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-3-methoxymethylindol-2-yl) sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

1-[(1-Acetyl-5-chloroindol-2-yl) sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(1-Acetyl-5-chloroindol-2-yl) sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine N-oxide

1-[(1-Acetyl-5-chloroindol-2-yl)]-4-[[5-(2-methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(1-Acetyl-5-chloroindol-2-yl) sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-methylpyridine N-oxide

1-[(5-Chloro-1-formylindol-2-yl) sulfonyl]-4-[[5-(pyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

4-[2-[[4-[(5-Chloro-1-formylindol-2-

yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]pyridine  
N-oxide

1-[(5-Chloro-1-formylindol-2-yl)]-4-[[5-(2-  
methylpyridin-4-yl)pyrimidin-2-yl]carboxy]piperazine

5 4-[2-[[4-[(5-Chloro-1-formylindol-2-  
yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-5-yl]-2-  
methylpyridine N-oxide

2,6-Bis[(N-methylcarbamoyl)methyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-  
10 yl)pyrimidin-2-yl]piperazine

2,6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-  
yl)pyrimidin-2-yl]piperazine

2,6-Bis[(morpholin-4-yl)carbonylmethyl]-4-[(6-  
15 chloronaphthalen-2-yl)sulfonyl]-1-[5-(pyridin-4-  
yl)pyrimidin-2-yl]piperazine

2,6-Bis(hydroxyethyl)-4-[(6-chloronaphthalen-2-  
yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

1-[(4-Chloro-2-hydroxystyryl)sulfonyl]-4-[5-(pyridin-4-  
20 yl)pyrimidin-2-yl]piperazine

2,6-Bis[(N-methylcarbamoyl)methyl]-4-[(4-chloro-2-  
hydroxystyryl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-  
yl]piperazine

2,6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(4-chloro-2-  
25 hydroxystyryl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-  
yl]piperazine



2,6-Bis[(morpholin-4-yl)carbonylmethyl]-4-[(4-chloro-2-hydroxystyryl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

5 2,6-Bis(hydroxyethyl)-4-[(4-chloro-2-hydroxystyryl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

2,6-Bis[(N-methylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

10 2,6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

2,6-Bis[(morpholin-4-yl)carbonylmethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

15 2,6-Bis(hydroxyethyl)-4-[(5-chloroindol-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

2,6-Bis[(N-methylcarbamoyl)methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

20 2,6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

25 2,6-Bis[(morpholin-4-yl)carbonylmethyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

2,6-Bis(hydroxyethyl)-4-[(6-chlorobenzo[b]thien-2-

yl)sulfonyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

4-[5-[[2,6-Bis(carbamoylmethyl)-4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

5 4-[5-[[2,6-Bis[(N-methylcarbamoyl)methyl]-4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

10

4-[5-[[2,6-Bis[(morpholin-4-yl)carbonylmethyl]-4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis(hydroxyethyl)-4-(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

15

4-[5-[[4-[(4-Chloro-2-hydroxystyryl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis(carbamoylmethyl)-4-[(4-chloro-2-

20

hydroxystyryl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis[(N-methylcarbamoyl)methyl]-4-[(4-chloro-2-hydroxystyryl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

25

4-[5-[[2,6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-[(4-chloro-2-hydroxystyryl)sulfonyl]piperazin-1-

yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis[(morpholin-4-yl)carbonylmethyl]-4-[(4-chloro-2-hydroxystyryl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

5 4-[5-[[2,6-Bis(hydroxyethyl)-4-[(4-chloro-2-hydroxystyryl)sulfonyl]piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis(carbamoylmethyl)-4-(5-chloroindol-2-ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine  
10 N-oxide

4-[5-[[2,6-Bis[(N-methylcarbamoyl)methyl]-4-(5-chloroindol-2-ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis[(N,N-dimethylcarbamoyl)methyl]-4-(5-chloroindol-2-ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide  
15

4-[5-[[2,6-Bis[(morpholin-4-yl)carbonylmethyl]-4-(5-chloroindol-2-ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

20 4-[5-[[2,6-Bis(hydroxyethyl)-4-(5-chloroindol-2-ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis(carbamoylmethyl)-4-(6-chlorobenzo[b]thien-2-ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide  
25

4-[5-[[2,6-Bis[(N-methylcarbamoyl)methyl]-4-(6-

chlorobenzo[b]thien-2-ylsulfonyl)piperazin-1-  
yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-bis[(N,N-dimethylcarbamoyl)methyl]-4-(6-  
chlorobenzo[b]thien-2-ylsulfonyl)piperazin-1-  
5 yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis[(morpholin-4-yl)carbonylmethyl]-4-(6-  
chlorobenzo[b]thien-2-ylsulfonyl)piperazin-1-  
yl]carbonyl]pyrimidin-2-yl]pyridine N-oxide

4-[5-[[2,6-Bis(hydroxyethyl)-4-(6-chlorobenzo[b]thien-2-  
10 ylsulfonyl)piperazin-1-yl]carbonyl]pyrimidin-2-yl]pyridine  
N-oxide

1-[(4-Chloro-2-hydroxystyryl)sulfonyl]-4-[5-(2-  
hydroxymethylpyridin-4-yl)pyrimidin-2-yl]piperazine

1-[(4-Chloro-2-hydroxystyryl)sulfonyl]-4-[5-(2-  
15 dimethylaminomethylpyridin-4-yl)pyrimidin-2-yl]piperazine

1-[(4-Chloro-2-hydroxystyryl)sulfonyl]-4-[5-(2-  
carbamoylpyridin-4-yl)pyrimidin-2-yl]piperazine

1-[(4-Chloro-2-hydroxystyryl)sulfonyl]-4-[4-(2-  
hydroxymethylpyridin-4-yl)benzoyl]piperazine

20 1-[(4-Chloro-2-hydroxystyryl)sulfonyl]-4-[4-(2-  
dimethylaminomethylpyridin-4-yl)benzoyl]piperazine

1-[(4-Chloro-2-hydroxystyryl)sulfonyl]-4-[4-(2-  
carbamoylpyridin-4-yl)benzoyl]piperazine

4-[(6-Chloronaphthalene-2-yl)sulfonyl]-2-[(N-  
25 methylcarbamoyl)methyl]-1-[5-(pyridin-4-yl)pyrimidin-2-  
yl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

5 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-hydroxyethyl-1-[5-(pyridin-4-yl)pyrimidin-2-yl]piperazine

10 3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-hydroxy-9-[4-(pyridin-4-yl)benzoyl]-3,9-diazabicyclo[3.3.1]nonane

4-[4-[[[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-hydroxy-3,9-diazabicyclo[3.3.1]nonan]-9-yl]carbonyl]phenyl]pyridine N-oxide

15 3-[(5-Chloroindol-2-yl)sulfonyl]-7-hydroxy-9-[4-(pyridin-4-yl)benzoyl]-3,9-diazabicyclo[3.3.1]nonane

4-[4-[[[3-[(5-Chloroindol-2-yl)sulfonyl]-7-hydroxy-3,9-diazabicyclo[3.3.1]nonan]-9-yl]carbonyl]phenyl]pyridine N-oxide

20 3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-7-hydroxy-9-[4-(pyridin-4-yl)benzoyl]-3,9-diazabicyclo[3.3.1]nonane

4-[4-[[[3-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-7-hydroxy-3,9-diazabicyclo[3.3.1]nonan]-9-yl]carbonyl]phenyl]pyridine N-oxide

25 3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-hydroxy-9-[[5-(pyridin-4-yl)pyrimidin-2-yl]carbonyl]-3,9-diazabicyclo[3.3.1]nonane

4-[2-[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-hydroxy-  
3,9-diazabicyclo[3.3.1]nonan-8-yl]carbonylpyrimidin-5-  
yl]pyridine N-oxide

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-methylamino-9-  
5 [4-(pyridin-4-yl)benzoyl]-3,9-diazabicyclo[3.3.1]nonane

4-[4-[[[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-  
methylamino-3,9-diazabicyclo[3.3.1]nonan]-9-  
yl]carbonyl]phenyl]pyridine N-oxide

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-dimethylamino-9-  
10 [4-(pyridin-4-yl)benzoyl]-3,9-diazabicyclo[3.3.1]nonane

4-[4-[[[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-  
dimethylamino-3,9-diazabicyclo[3.3.1]nonan]-9-  
yl]carbonyl]phenyl]pyridine N-oxide

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-piperidino-9-[4-  
15 (pyridin-4-yl)benzoyl]-3,9-diazabicyclo[3.3.1]nonane

4-[4-[[[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-  
piperidino-3,9-diazabicyclo[3.3.1]nonan]-9-  
yl]carbonyl]phenyl]pyridine N-oxide

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-morpholino-9-[4-  
20 (pyridin-4-yl)benzoyl]-3,9-diazabicyclo[3.3.1]nonane

4-[4-[[[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-  
morpholino-3,9-diazabicyclo[3.3.1]nonan]-9-  
yl]carbonyl]phenyl]pyridine N-oxide

3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-(4-  
25 methylpiperazin-1-yl)-9-[4-(pyridin-4-yl)benzoyl]-3,9-  
diazabicyclo[3.3.1]nonane

4-[4-[[[3-[(6-Chloronaphthalen-2-yl)sulfonyl]-7-(4-methylpiperazin-1-yl)-3,9-diazabicyclo[3.3.1]nonan]-9-yl]carbonyl]phenyl]pyridine N-oxide

5 1-[[ (6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[[ (6RS)-6-Aminomethyl-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

10 1-[[ (2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[[ (2RS)-6-Aminomethyl-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

15 1-[(7-Aminomethylnaphthalen-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[(7-Aminomethylnaphthalen-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

1-[(6-Aminomethylnaphthalen-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

20 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(isoquinolin-7-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(quinolyl-2-yl)carbonyl]piperazine

25 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4-hydroxyquinolin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(8-

hydroxyquinolin-7-yl) carbonyl]piperazine

1-[(Benzimidazol-5-yl) carbonyl]-4-[(6-chloronaphthalen-2-yl) sulfonyl]piperazine

1-[(Benzimidazol-5-yl) carbonyl]-4-[(6-chloronaphthalen-2-yl) sulfonyl]homopiperazine

1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

1-[(E)-4-Chlorostyrylsulfonyl]-4-[(thiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]piperazine

1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[trans-3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]piperazine

1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]piperazine

1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propyl]piperazine

1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[N-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]carbamoyl]piperazine

1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl) carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl) sulfonyl]-2-ethoxycarbonyl-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl) carbonyl]piperazine



2-Carboxy-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-  
 [(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
 yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-  
 5 aminohydroxyiminomethyl-4,5,6,7-tetrahydrothieno[3,2-  
 c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-(4,5,6,7-  
 tetrahydrothieno[3,2-c]pyridin-2-yl)carbamoyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[N-methy-N-  
 10 (4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
 yl)carbamoyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[5-(1-pyrrolin-  
 2-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
 yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-  
 15 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-  
 aminohydroxyiminomethyl-4,5,6,7-tetrahydrothiazolo[5,4-  
 c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Carbamoyl-4,5,6,7-tetrahydrothiazolo[5,4-  
 20 c]pyridin-2-yl)carbonyl]-4-[(6-chloronaphthalen-2-  
 yl)sulfonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(1-pyrrolin-  
 2-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 25 yl]carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-formyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
5 yl)carbonyl]piperazine

2-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-  
yl)carbonyl]-6,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridinium iodide

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-  
10 yl)carbonyl]-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-N-oxide

2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-  
[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

2-Carbamoyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-  
15 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(2-  
hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
20 yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-2-  
yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-3-  
25 yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[[6-(pyridin-4-yl)methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl]carbonyl]piperazine

1-[(E)-4-Chlorostyrylsulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(E)-4-Chlorostyrylsulfonyl]-4-[6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

(3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamide]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]pyrrolidine

(3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamide]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]pyrrolidine

(3S)-1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-[[4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]amino]pyrrolidine

(3S)-3-[(4,5,6,7-Tetrahydrothieno[3,2-c]pyridin-2-yl)carbonylamino]-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]homopiperazine

4-[(6-Chloronaphthalen-2-yl)sulfonamide]-1-[(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)carbonyl]piperidine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-aminohydroxyiminomethylbenzofuran-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-

aminohydroxyiminomethylbenzothiophen-2-  
yl) carbonyl] piperazine

1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[(1,2,3,4-  
tetrahydroisoquinolin-6-yl) carbonyl] piperazine

5 1-[(6-Chloronaphthalen-2-yl) sulfonyl]-4-[(2-methyl-  
1,2,3,4-tetrahydroisoquinolin-6-yl) carbonyl] piperazine

6-[[4-[(6-Chloronaphthalen-2-yl) sulfonyl] piperazin-1-  
yl] carbonyl]-2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium  
iodide

10 1-[(5-Chloroindol-2-yl) sulfonyl]-4-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl] piperazine

4-[(5-Chloroindol-2-yl) sulfonyl]-2-(N-methylcarbamoyl)-  
1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl) carbonyl] piperazine

15 4-[(5-Chloroindol-2-yl) sulfonyl]-2-(N-methylcarbamoyl)-  
1-[(6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridin-2-  
yl) carbonyl] piperazine

1-[(5-Chlorobenzo[b]furan-2-yl) sulfonyl]-4-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
20 yl) carbonyl] piperazine

1-[(6-Chlorobenzo[b]furan-2-yl) sulfonyl]-4-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl) carbonyl] piperazine

1-[(5-Chlorobenzo[b]thien-2-yl) sulfonyl]-4-[(6-methyl-  
25 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl) carbonyl] piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5,6,7,8-  
5 tetrahydro-1,6-naphthylidin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-  
5,6,7,8-tetrahydro-1,6-naphthylidin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(4,5,6,7-  
10 tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-  
4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-  
yl)carbonyl]piperazine

15 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-ethyl-  
4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(1-methyl-  
4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-  
20 yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(1,5-dimethyl-  
4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(6-methyl-  
25 4,5,6,7-tetrahydrofro[2,3-c]pyridin-2-  
yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(3-hydroxy-6-methyl-4,5,6,7-tetrahydrofro[2,3-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-3-hydroxy-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydroxazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis(carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

cis-2,6-Bis(carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroisindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
[[ (morpholin-4-yl) carbonyl]methyl]piperazine

5 N-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-yl]carbonyl]glycine ethyl ester

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
[N-(morpholin-4-yl) carbamoyl]piperazine

10 Ethyl N'-[[4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-  
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetate

15 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
[N-[[ (morpholin-4-yl) carbonyl]methyl] carbamoyl]piperazine

4-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-yl]carbonyl]morpholine

20 4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-  
(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

Methyl [4-[(6-chloronaphthalen-2-yl)sulfonyl]-1-[(6-  
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-yl]acetate

25 2-[[N-(tert-Butoxy) amino] carbonyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 [4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazin-2-yl]acetamide

5        4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(N-  
 isopropyl)carbamoyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[piperidin-1-  
 yl)carbonyl]methyl]-1-[(6-methyl-4,5,6,7-

10 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-  
 methoxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-  
 15 methoxyethyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazine-2-carboxylic acid

20        N'-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazin-2-yl]carbonyl]hydrazinoacetic acid

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

25 [[N-(tetrahydropyran-2-yloxy)]carbamoyl]piperazine

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-1-[(6-methyl-



4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-hydroxamic acid

4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[[N-(2-hydroxybenzyl)]carbamoyl]-1-[(6-methyl-4,5,6,7-

5 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Bromonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 1-[(7-Amidinonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Amidinonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[7-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

20 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]piperazine

1-[(7-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

25 1-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Ethynylnaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 1-[(5-Bromoindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Amidinoindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 1-[(6-Amidinoindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 1-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-

20 yl]sulfonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]piperazine

25 1-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Amidinobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 1-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[[6-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

15 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

20 4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

25 4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

5 2-[[4-[(5-Bromoindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

10 2-[[2-(Carbamoyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-(Carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

15 2-[[2,6-Bis(carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

20 2-[[2-[[[(Tetrazol-5-ylmethyl)amino]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-[2-(Tetrazol-5-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

25 2-[[2-[(Morpholin-4-ylcarbonyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(carbamoylmethyl)-1-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 5 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-  
 dimethylcarbamoylmethyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [[(tetrazol-5-yl)amino]carbonyl]piperazine

10 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [[(tetrazol-5-ylmethyl)amino]carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 15 [[(tetrazol-5-ylamino)carbonyl]methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [[[(tetrazol-5-ylmethyl)amino]carbonyl]methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 20 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 (tetrazol-5-ylmethyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-  
 (tetrazol-5-yl)ethyl]piperazine

25 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-  
 methylcarbamoylmethyl)-1-[(6-methyl-4,5,6,7-

- tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(morpholin-4-ylcarbonyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
- 5 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[(morpholin-4-ylcarbonyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
- 4-[(5-Ethynylisoindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
- 10 4-[(5-Chloroisoindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
- 2-(Carbamoylmethyl)-4-[(5-chloroisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
- 15 2-(Carbamoylmethyl)-4-[(5-ethynylisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
- 20 4-[(5-Chloroisoindol-2-yl)sulfonyl]-2-(N-methylcarbamoylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine
- 4-[(5-Chloroisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine
- 25 4-[(5-Chloroisoindol-2-yl)sulfonyl]-1-[(6-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(5-Bromoisindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

5 (morpholinocarbonylmethyl)piperazine

4-[(5-Ethynylisindol-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
[(morpholin-4-ylcarbonyl)methyl]piperazine

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[(5-methyl-  
10 4,5,6,7-tetrahydroxazolo[4,5-c]pyridin-2-  
yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-  
1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-  
2-yl)carbonyl]piperazine

15 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-  
methylcarbamoylmethyl)-1-[(6,7-dimethyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-  
(morpholinocarbonylmethyl)-1-[(6,7-dimethyl-4,5,6,7-  
20 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-  
(morpholinocarbonylmethyl)-1-[(6,7-dimethyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Bromoindol-2-yl)sulfonyl]-2-  
25 (morpholinocarbonylmethyl)-1-[(6,7-dimethyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis(carbamoylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis(carbamoylmethyl)-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[ethoxycarbonylmethyl]aminocarbonyl]methyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[ethoxycarbonylmethyl]aminocarbonyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[carboxymethyl]aminocarbonyl]methyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[carboxymethyl]aminocarbonyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-



4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [[[(tetrazol-5-yl)methyl]aminocarbonyl]methyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 5 [[[(tetrazol-5-yl)methyl]aminocarbonyl]methyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [(tetrazol-5-yl)methyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 10 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [(tetrazol-5-yl)methyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [2-(tetrazol-5-yl)ethyl]piperazine  
 15 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-  
 (tetrazol-5-yl)ethyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 20 [(2-oxopyrrolidin-1-yl)methyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(2-  
 oxopyrrolidin-1-yl)methyl]piperazine  
 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-  
 25 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [2-(2-oxopyrrolidin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxopyrrolidin-1-yl)ethyl]piperazine

5 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(4-hydroxy-2-oxopyrrolidin-1-yl)methyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(4-hydroxy-2-oxopyrrolidin-1-yl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(4-hydroxy-2-oxopyrrolidin-1-yl)ethyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(4-hydroxy-2-oxopyrrolidin-1-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(2,5-dioxopyrrolidin-1-yl)methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(2,5-dioxopyrrolidin-1-yl)methyl]piperazine

20 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

25 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2,5-

dioxopyrrolidin-1-yl)ethyl]piperazine

2,6-Bis[2-(4-hydroxy-2-oxopyrrolidin-1-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 2,6-Bis[2-(2-oxopyrrolidin-1-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis[2-(tetrazol-5-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 2,6-Bis[(tetrazol-5-yl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2,6-Bis[(N-methylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 2,6-Bis[(2,5-dioxopyrrolidin-1-yl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20 2,6-Bis[2-(2,5-dioxopyrrolidin-1-yl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6,7-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

25 4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-4-[[7-[N-(methoxycarbonyl)amidino]naphthalen-  
2-yl]sulfonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-  
2-yl]sulfonyl]piperazine-2-carboxylic acid

4-[(7-[(Amino)(hydroxyimino)methyl]naphthalen-2-  
yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-  
yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-  
2-carboxylic acid

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-  
2-carboxylic acid

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-  
1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine-2-carboxylic acid

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-  
1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine-2-carboxylic acid

5 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine-2-carboxylic acid

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

10 4-[(6-amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

15 1-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

4-[[6-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine-2-carboxylic acid

20 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine-2-carboxylic acid

25 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-(N-methoxycarbonylamidino)benzo[b]thien-2-yl)sulfonyl]piperazine-2-carboxylic acid

4-[(5-Amidinoisindol-2-yl)sulfonyl]-1-[(6-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine-2-carboxylic acid

4-[[5-[(Amino) (hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine-2-carboxylic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]piperazine-2-carboxylic acid

4-[(7-Amidinonaphthalen-2-yl) sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl) sulfonyl] -2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[7-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]piperazine

4-[(7-[(Amino) (hydroxyimino)methyl]naphthalen-2-yl) sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(6-[(Amino) (hydroxyimino)methyl]naphthalen-2-

yl) sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino) (hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 4-[[6-[(Amino) (hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]piperazine

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2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]piperazine

15 4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino) (hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-2-(ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

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2-(Ethoxycarbonyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]piperazine

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

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4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl) carbonyl]-4-[[5-(N-methoxycarbonylamidino) indol-2-yl]sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[6-[N-(methoxycarbonyl) amidino] indol-2-yl]sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl) sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[[5-[(Amino) (hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[5-[N-(methoxycarbonyl) amidino]benzo[b]thien-2-yl]sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[(5-Amidinoisoindol-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[[5-[(Amino) (hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[(tetrazol-5-yl)methyl]piperazine

4-[[5-[N-(Methoxycarbonyl) amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[(tetrazol-5-

yl)methyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

5 2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(tetrazol-5-yl)methyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
10 [2-(tetrazol-5-yl)ethyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
[2-(tetrazol-5-yl)ethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine  
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4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine  
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4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine  
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4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

10 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl]sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

5 4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

10 4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

15 2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

20 4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

25 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl)sulfonyl]-2-[N-[(tetrazol-5-

yl)methyl]carbamoyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-

5 yl)methyl]carbamoyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

15 4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl]sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

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1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

5        4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

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1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

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4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

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4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoyl]piperazine

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2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[N-  
 [(tetrazol-5-yl)methyl]carbamoyl]piperazin-1-yl]carbonyl]-  
 6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[N-[(tetrazol-5-  
 5 yl)methyl]carbamoyl]piperazin-1-yl]carbonyl]-6-  
 methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

10 4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-  
 15 2-yl]sulfonyl]-2-[N-[(tetrazol-5-  
 yl)methyl]carbamoylmethyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-  
 yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
 c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-  
 20 yl)methyl]carbamoylmethyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-  
 [(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
 25 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-  
 [(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine



4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

5 4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

10 4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

15 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl]sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

20 4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

25 4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylmethyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

5 4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

10

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazine

15

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[N-[(tetrazol-5-yl)methyl]carbamoylemethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

20

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

25 4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-(Ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-

5 yl]sulfonyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-

yl) sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(5-Ethynylindol-2-yl) sulfonyl]-2-

10 (ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(5-Amidinoindol-2-yl) sulfonyl]-2-

(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

15 4-[(6-Amidinoindol-2-yl) sulfonyl]-2-

(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl] sulfonyl]-

2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-

20 tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl] sulfonyl]-

2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

25 yl) carbonyl]-2-(ethoxycarbonylmethyl)-4-[[5-(N-

methoxycarbonylamidino)indol-2-yl] sulfonyl]piperazine

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(ethoxycarbonylmethyl)-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl]sulfonyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-

5 (ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl]sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(ethoxycarbonylmethyl)-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-

15 (ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-2-(ethoxycarbonylmethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20 2-(Ethoxycarbonylmethyl)-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-

25 (ethoxycarbonylmethyl)piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-(ethoxycarbonylmethyl)piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

5 4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

10 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]piperazin-2-acetic acid

15 4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

20 4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

25 4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazin-2-acetic acid

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-  
1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-acetic acid

5 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-  
yl]sulfonyl]piperazin-2-acetic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-  
10 yl]sulfonyl]piperazin-2-acetic acid

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-acetic acid

4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-  
15 yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-4-[[5-[N-  
(methoxycarbonyl)amidino]benzo[b]thien-2-  
20 yl]sulfonyl]piperazin-2-acetic acid

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-acetic acid

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-  
25 yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-acetic acid

2-[[2-(Carboxymethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-(Carboxymethyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

10 4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]piperazine

20 4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 4-[(6-Amidinoindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(N-methylcarbamoyl)methyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl)sulfonyl]piperazine

2-[(N-Methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-yl)sulfonyl]piperazine

20 4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

25 4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[(N-Methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-



tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-2-[(N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[(N-methylcarbamoyl)methyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[2-[(N-Methylcarbamoyl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

2-[[2-[(N-methylcarbamoyl)methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl)methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl)methyl]-4-[(6-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[ [N-(Ethoxycarbonylmethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[6-[N-(methoxycarbonyl) amidino]naphthalen-2-yl]sulfonyl]piperazine

4-[(6-[(Amino) (hydroxyimino)methyl]naphthalen-2-yl) sulfonyl]-2-[ [N-(ethoxycarbonylmethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(5-Ethynylindol-2-yl) sulfonyl]-2-[ [N-(ethoxycarbonylmethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(5-Amidinoindol-2-yl) sulfonyl]-2-[ [N-(ethoxycarbonylmethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(6-Amidinoindol-2-yl) sulfonyl]-2-[ [N-(ethoxycarbonylmethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[ [5-[(Amino) (hydroxyimino)methyl]indol-2-yl]sulfonyl]-2-[ [N-(ethoxycarbonylmethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-  
2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

5 2-[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-  
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-  
yl]sulfonyl]piperazine

10 2-[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-  
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-  
yl]sulfonyl]piperazine

15 4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-[[N-  
(ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

20 4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-  
yl]sulfonyl]-2-[[N-(ethoxycarbonylmethyl)carbamoyl]methyl]-  
1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

25 2-[[N-(Ethoxycarbonylmethyl)carbamoyl]methyl]-1-[(6-  
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-4-[[5-[N-  
(methoxycarbonyl)amidino]benzo[b]thien-2-  
yl]sulfonyl]piperazine

4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-[[N-

(ethoxycarbonylmethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[[5-[(Amino) (hydroxyimino)methyl]isoindol-2-yl]sulfonyl]-2-[[N-(ethoxycarbonylmethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[[N-(Ethoxycarbonylmethyl) carbamoyl]methyl]-4-[[5-[N-(methoxycarbonyl) amidino]isoindol-2-yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl) sulfonyl]-2-[[N-(ethoxycarbonylmethyl) carbamoyl]methyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl) sulfonyl]-2-[[N-(carboxymethyl) carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(6-Amidinonaphthalen-2-yl) sulfonyl]-2-[[N-(carboxymethyl) carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[[N-(Carboxymethyl) carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-4-[[6-[N-(methoxycarbonyl) amidino]naphthalen-2-yl]sulfonyl]piperazine

4-[(6-[(Amino) (hydroxyimino)methyl]naphthalen-2-yl) sulfonyl]-2-[[N-(carboxymethyl) carbamoyl]methyl]-1-[(6-

methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Carboxymethyl)carbamoyl]methyl]-4-[(5-ethyny lindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Amidinoindol-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-yl]sulfonyl]piperazine

2-[[N-(Carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-

yl)sulfonyl]piperazine

4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[5-[N-(methoxycarbonyl)amidino]benzo[b]thien-2-yl)sulfonyl]piperazine

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4-[(5-Amidinoisoindol-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

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4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-yl)sulfonyl]-2-[[N-(carboxymethyl)carbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-(Carboxymethyl)carbamoyl]methyl]-4-[[5-[N-(methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

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2-[[2-[[N-(Carboxymethyl)carbamoyl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

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2-[[2-[[N-(Carboxymethyl)carbamoyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(7-Amidinonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(6-Amidinonaphthalen-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

10 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]naphthalen-2-yl]sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(6-[(Amino)(hydroxyimino)methyl]naphthalen-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

20 4-[(5-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(6-Amidinoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

25 4-[[5-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-

1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine  
 4-[[6-[(Amino)(hydroxyimino)methyl]indol-2-yl]sulfonyl]-  
 1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 5 yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine  
 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-4-[[5-(N-methoxycarbonylamidino)indol-2-  
 yl]sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine  
 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 10 yl)carbonyl]-4-[[6-[N-(methoxycarbonyl)amidino]indol-2-  
 yl]sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine  
 4-[(5-Amidinobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [(morpholin-4-yl)carbonylmethyl]piperazine  
 15 4-[[5-[(Amino)(hydroxyimino)methyl]benzo[b]thien-2-  
 yl]sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
 c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-  
 yl)carbonylmethyl]piperazine  
 1-[(6-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 20 yl)carbonyl]-4-[[5-[N-  
 (methoxycarbonyl)amidino]benzo[b]thien-2-yl]sulfonyl]-2-  
 [(morpholin-4-yl)carbonylmethyl]piperazine  
 4-[(5-Amidinoisoindol-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 25 [(morpholin-4-yl)carbonylmethyl]piperazine  
 4-[[5-[(Amino)(hydroxyimino)methyl]isoindol-2-



yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[[5-[N-(Methoxycarbonyl)amidino]isoindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

2-[[4-[(6-Chloronaphthalen-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazin-1-yl]carbonyl]-6-

methylthiazolo[5,4-c]pyridinium iodide

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazin-1-yl]carbonyl]-6-methylthiazolo[5,4-c]pyridinium iodide

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-cyano-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

1-[(7-Carbamoyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-dimethylamino-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2,5-dioxopyrrolidin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-cyano-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

1-[(7-Carbamoyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-dimethylamino-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(tetrazol-5-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-cyano-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[[(ethoxycarbonyl)methyl]amino]carbonyl]methyl]piperazine

10 1-[(7-Carbamoyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-

[[[(ethoxycarbonyl)methyl]amino]carbonyl]methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(7-dimethylamino-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

[[[(ethoxycarbonyl)methyl]amino]carbonyl]methyl]piperazine

2-[[[(Carboxymethyl)amino]carbonyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(7-cyano-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(7-Carbamoyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-

[[[(carboxymethyl)amino]carbonyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

25 2-[[[(Carboxymethyl)amino]carbonyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(7-dimethylamino-6-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[7-  
[(dimethylamino)methyl]benzothiazol-2-yl)carbonyl]-2-(N-  
5 methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[7-  
[(dimethylaminomethyl)methyl]thiazolo[5,4-c]pyridin-2-  
yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[7-  
10 [(dimethylamino)methyl]-4,5,6,7-tetrahydrobenzothiazol-2-  
yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-  
1-[7-[(morpholin-4-yl)methyl]benzothiazol-2-  
yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-  
15 1-[6-(morpholin-4-yl)-4,5,6,7-tetrahydrobenzothiazol-2-  
yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-  
1-[7-(piperidin-1-yl)benzothiazol-2-yl)carbonyl]piperazine

20 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-  
1-[6-(piperidin-1-yl)-4,5,6,7-tetrahydrobenzothiazol-2-  
yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(2-methyl-  
4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-5-  
25 yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(2-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-5-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methoxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(morpholin-4-ylcarbonyl)methyl]-1-[(6-sulfo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-sulfo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonyl)methyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl)methyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine

5 4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

10 1-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

15 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

1-[(5,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

20 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

1-[(5,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

2-[(N,N-Dimethylcarbamoyl)methyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

2-[(N,N-Dimethylcarbamoyl)methyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

2-(2-Cyanoethyl)-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

5 2-(2-Cyanoethyl)-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

10 4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

20 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

1-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

2-(2-Cyanoethyl)-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

2-[(N,N-Dimethylcarbamoyl)methyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine

4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine



1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

1-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

5 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

1-[(5,6-Dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

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4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

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4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

20 1-[(5,6-Dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-4-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

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2-[(N,N-Dimethylcarbamoyl)methyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

5 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

2-[(N,N-Dimethylcarbamoyl)methyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine

10 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

2-(2-Cyanoethyl)-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

15 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

2-(2-Cyanoethyl)-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

20 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

5 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

4-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

10 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

15 1-[(6-Ethynylbenzo[b]thien-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

20 2-(2-Cyanoethyl)-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

2-[(N,N-Dimethylcarbamoyl)methyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(5,6-dihydrobenzo[f]isoquinolin-8-yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(5,6-dihydropyrido[4,3-f]quinazolin-3-yl)carbonyl]piperazine

8-[[1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-4-yl]carbonyl]-5,6-dihydrobenzo[f]isoquinoline N-oxide

3-[[1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazin-4-yl]carbonyl]-5,6-dihydropyrido[4,3-f]quinazoline N-oxide

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methanesulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methanesulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methanesulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(morpholin-4-ylcarbonylmethyl)piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-methanesulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methanesulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methanesulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methanesulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(morpholin-4-ylcarbonylmethyl)piperazine

10 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-methanesulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl)carbonyl]piperazine

15 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-6-yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(2-dimethylamino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-yl)carbonyl]piperazine

20 4-[(6-Chlorobenzo[b]thiophen-2-yl)sulfonyl]-1-[(6-methyl-5-oxo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(6-Chlorobenzo[b]thiophen-2-yl)sulfonyl]-1-[(6-methyl-5-oxo-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

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4-[(6-Chlorobenzo[b]thiophen-2-yl)sulfonyl]-1-[(5-oxo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

5 4-[(6-Chlorobenzo[b]thiophen-2-yl)sulfonyl]-1-[(5-oxo-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

10 1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

15 1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

20 1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)piperazine.

5 1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]piperazine.

10 1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-4-[(6-ethynylbenzo[b]thien-2-yl)sulfonyl]piperazine.

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(2-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-5-yl)carbonyl]piperazine

15 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(2-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-5-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

20 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(2-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-5-yl)carbonyl]piperazine

25 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-5-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(2-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-5-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

5 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(5-methyl-4,5,6,7-tetrahydropyrrolo[3,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methoxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

10 4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methoxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(morpholin-4-ylcarbonyl)methyl]-1-[(6-sulfo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-sulfo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[(morpholin-4-ylcarbonyl)methyl]-1-[(6-sulfo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-piperazine

2-(2-Cyanoethyl)-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-sulfo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine



4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

5 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine  
 10 1-[(5,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.  
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1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine  
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1-[(5,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-  
1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-  
yl)carbonyl]piperazine.

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-  
5 1-[(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-  
yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(5,6-dimethyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-  
2-(N-methylcarbamoyl)piperazine  
10 1-[(5,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridazin-2-yl)carbonyl]-4-[(5-ethynylindol-2-  
yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N,N-  
dimethylcarbamoyl)methyl]-1-[(4,5,6,7-  
15 tetrahydrothiazolo[5,4-c]pyridazin-2-  
yl)carbonyl]piperazine.

2-[(N,N-Dimethylcarbamoyl)methyl]-4-[(5-ethynylindol-2-  
yl)sulfonyl]-1-[(4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridazin-2-yl)carbonyl]piperazine.

20 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N,N-  
dimethylcarbamoyl)methyl]-1-[(5,6-dimethyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

2-[(N,N-Dimethylcarbamoyl)methyl]-1-[(5,6-dimethyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-  
25 4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-  
 [(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-  
 yl)carbonyl]piperazine.

2-(2-Cyanoethyl)-4-[(5-ethynylindol-2-yl)sulfonyl]-1-  
 5 [(4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-2-  
 yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-  
 [(5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridazin-  
 2-yl)carbonyl]piperazine

10 2-(2-Cyanoethyl)-1-[(5,6-dimethyl-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(5-  
 ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-  
 15 methylcarbamoyl)piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-  
 methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-  
 20 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [[(morpholin-4-yl)carbonyl]methyl]piperazine.

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [[(morpholin-4-yl)carbonyl]methyl]piperazine.

25 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

2-(2-Cyanoethyl)-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

2-[(N,N-Dimethylcarbamoyl)methyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine.

5 1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine.

1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]piperazine.

15 1-[(6-Amino-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

20 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine

1-[(5,6-Dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-2-[[morpholin-4-yl)carbonyl)methyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

1-[(5,6-Dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

1-[(5,6-Dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

2-[(N,N-Dimethylcarbamoyl)methyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

2-[(N,N-Dimethylcarbamoyl)methyl]-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

2-(2-Cyanoethyl)-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]piperazine

2-(2-Cyanoethyl)-1-[(5,6-dimethyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridazin-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

5 4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N-methylcarbamoyl)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

10 4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[[ (morpholin-4-yl)carbonyl]methyl]piperazine.

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

15 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

20 2-(2-Cyanoethyl)-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N,N-dimethylcarbamoyl)methyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

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2-[(N,N-Dimethylcarbamoyl)methyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-hydroxy-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine.

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(5,6-dihydrobenzo[f]isoquinolin-8-yl)carbonyl]piperazine

1-[(5,6-Dihydrobenzo[f]isoquinolin-8-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(5,6-dihydropyrido[4,3-f]quinazolin-3-yl)carbonyl]piperazine

1-[(5,6-Dihydropyrido[4,3-f]quinazolin-3-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

8-[[1-[(5-Chloroindol-2-yl)sulfonyl]piperazin-4-yl]carbonyl]-5,6-dihydrobenzo[f]isoquinoline N-oxide

8-[[1-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-4-yl]carbonyl]-5,6-dihydrobenzo[f]isoquinoline N-oxide

3-[[1-[(5-Chloroindol-2-yl)sulfonyl]piperazin-4-yl]carbonyl]-5,6-dihydropyrido[4,3-f]quinazoline N-oxide

3-[[1-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-4-yl]carbonyl]-5,6-dihydropyrido[4,3-f]quinazoline N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[4,5-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-oxo-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-hydroxyimino-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

5 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-ethylenedioxy-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]furan-2-yl)carbonyl]piperazine

10 1-[(6-Acetoxy-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methoxy-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

1-[(6-Amino-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

15 1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-dimethylamino-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[[6-(pyrrolidin-1-yl)-4,5,6,7-tetrahydrobenzothiazol-2-yl]carbonyl]piperazine

20 1-[(6-Acetylamino-1-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-oxo-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-hydroxyimino-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

25 1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-hydroxy-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

1-[(6-Ethylenedioxy-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothiazolo[5,4-c]furan-2-yl)carbonyl]piperazine

5 1-[(6-Acetoxy-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methoxy-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]piperazine

10 1-[(6-Amino-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

1-[(6-Dimethylamino-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[[6-(pyrrolidin-1-yl)-4,5,6,7-tetrahydrobenzothiazol-2-yl]carbonyl]piperazine

15 1-[(6-Acetylamino-4,5,6,7-tetrahydrobenzothiazol-2-yl)carbonyl]-4-[(5-ethynylindol-2-yl)sulfonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-5-oxo-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

20 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-5-oxo-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]-1-[(5-oxo-4,5,6,7-

25 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(morpholin-4-yl)carbonylmethyl]-1-[(5-oxo-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4-methyl-4,5,6,7-tetrahydrothieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(thieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thieno[3,2-b]pyridine N-oxide

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(4,5,6,7-tetrahydrothieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(4-methyl-4,5,6,7-tetrahydrothieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(thieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(5-Ethynylindol-2-yl)sulfonyl]piperazin-1-yl]carbonyl]thieno[3,2-b]pyridine N-oxide

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(4,5,6,7-tetrahydrothieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(4-methyl-4,5,6,7-tetrahydrothieno[3,2-b]pyridin-2-

yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-  
 [(thieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-  
 cyanoethyl)piperazin-1-yl]carbonyl]thieno[3,2-b]pyridine N-  
 5 oxide

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-  
 [(4,5,6,7-tetrahydrothieno[3,2-b]pyridin-2-  
 yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-  
 10 [(4-methyl-4,5,6,7-tetrahydrothieno[3,2-b]pyridin-2-  
 yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-  
 [(thieno[3,2-b]pyridin-2-yl)carbonyl]piperazine

2-[[4-[(5-Ethynylindol-2-yl)sulfonyl]-2-  
 15 (cyanoethyl)piperazin-1-yl]carbonyl]thieno[3,2-b]pyridine  
 N-oxide

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4,5,6,7-  
 tetrahydrothiazolo[5,4-c]pyridin-6-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(4,5,6,7-  
 20 tetrahydrothiazolo[5,4-c]pyridin-6-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(4,5,6,7-  
 tetrahydrooxazolo[5,4-c]pyridin-6-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(4,5,6,7-  
 tetrahydrooxazolo[5,4-c]pyridin-6-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(2-dimethylamino-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-6-  
yl)carbonyl]piperazine

5 1-[(2-Dimethylamino-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-6-yl)carbonyl]-4-[(5-ethynylindol-2-  
yl)sulfonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methylsulfonyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

10 4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
(N-methylcarbamoyle)piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
15 (morpholin-4-ylcarbonylmethyl)piperazine

2-(2-Cyanoethyl)-4-[(5-ethynylindol-2-yl)sulfonyl]-1-  
[(6-methylsulfonyl-4,5,6,7-tetrahydrothiazolo[5,4-  
c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-4-[(6-methylsulfonyl-  
20 4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-  
4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
(N-methylcarbamoyle)piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(morpholin-4-ylcarbonylmethyl)piperazine

5 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Ethynylindol-2-yl)sulfonyl]-4-[(6-methylsulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-(N-methylcarbamoyl)-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(morpholin-4-ylcarbonylmethyl)piperazine

2-(2-Cyanoethyl)-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methylsulfonyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxopyridin-1-yl)ethyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxopyridin-1-yl)ethyl]piperazine

5 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-[(coumarin-7-yl)oxy]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-[(coumarin-7-yl)oxy]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-[(cyclopropylcarbonyl)amino]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-[(cyclopropylcarbonyl)amino]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[[(cyclopropylcarbonyl)amino]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[[(cyclopropylcarbonyl)amino]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine



4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-cyanomethyl-N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(N-cyanomethyl-N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 2-(3-Butynyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(3-Butynyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[N-(2-hydroxyethyl)carbamoyl)methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[N-(2-hydroxyethyl)carbamoyl)methyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N,N-Bis(2-hydroxyethyl)carbamoyl)methyl]-1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N,N-Bis(2-hydroxyethyl)carbamoyl]methyl]-1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N,N-Bis(2-methoxyethyl)carbamoyl]methyl]-1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N,N-Bis(2-methoxyethyl)carbamoyl]methyl]-1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[N-(2-hydroxyethyl)-N-methylcarbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[[N-(2-hydroxyethyl)-N-methylcarbamoyl]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-Benzyl-N-(2-hydroxyethyl)carbamoyl]methyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[ [N-Benzyl-N-(2-hydroxyethyl) carbamoyl]methyl]-4-[(6-chlorobenzo[b]thien-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[2-[(morpholin-4-yl) carbonyl]ethyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl) sulfonyl]-2-[2-(dimethylaminocarbonyl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

10 4-[(6-Chlorobenzo[b]thien-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[2-[(pyrrolidin-1-yl) carbonyl]ethyl]piperazine

2-[2-(Aminosulfonyl)ethyl]-4-[(6-chlorobenzo[b]thien-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[2-[(morpholin-4-yl) sulfonyl]ethyl]piperazine

2-[2-[(t-Butoxycarbonylamino) sulfonyl]ethyl]-4-[(6-chlorobenzo[b]thien-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[2-[(n-Butoxycarbonylamino) sulfonyl]ethyl]-4-[(6-chlorobenzo[b]thien-2-yl) sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(ethoxycarbonylamino)sulfonyl]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(Acetylamino)sulfonyl]ethyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Aminosulfonylmethyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)sulfonylmethyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(pyrrolidin-1-yl)sulfonylmethyl]piperazine

2-[(t-Butoxycarbonylamino)sulfonylmethyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[(n-Butoxycarbonylamino)sulfonylmethyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[(ethoxycarbonylamino)sulfonylmethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[ (Acetylamino) sulfonylmethyl]-4-[ (6-chlorobenzo[b]thien-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[3-[ (4H-5-Acetoxy-4-oxo)pyran-2-yl]propyl]-4-[ (6-chlorobenzo[b]thien-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[ (6-Chlorobenzo[b]thien-2-yl) sulfonyl]-2-[3-[ (4H-5-hydroxy-4-oxo)pyran-2-yl]propyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[ (6-Chlorobenzo[b]thien-2-yl) sulfonyl]-2-[3-[ (4H-5-methoxy-4-oxo)pyran-2-yl]propyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

N-methyl-N-[ [4-[ (6-chlorobenzo[b]thien-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazin-2-yl]acetyl]methanesulfonamide

N-[ [4-[ (6-Chlorobenzo[b]thien-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazin-2-yl]acetyl]benzenesulfonamide

N-[2-[4-[ (6-Chlorobenzo[b]thien-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine-2-yl]ethyl]trifluoromethanesulfonamide

N-methyl-N-[2-[4-[ (6-chlorobenzo[b]thien-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazin-2-yl]ethyl]trifluoromethanesulfonamide

N-[4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetyl]-N'-methanesulfonylhydrazine

5        4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10       4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15       4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20       4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

25       4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 4-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

15 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-1,3-oxazolan-3-yl)ethyl]piperazine

20 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxopyridin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxopyridin-1-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-[(coumarin-7-yl)oxy]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-[(coumarin-7-yl)oxy]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-[(cyclopropylcarbonyl)amino]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-[(cyclopropylcarbonyl)amino]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[[(cyclopropylcarbonyl)amino]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[[(cyclopropylcarbonyl)amino]methyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(Aminosulfonyl)ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-[(morpholin-4-yl)sulfonyl]ethyl]piperazine



2-[2-[(t-Butoxycarbonylamino)sulfonyl]ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-[(n-Butoxycarbonylamino)sulfonyl]ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(ethoxycarbonylamino)sulfonyl]ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(Acetylamino)sulfonyl]ethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(Aminosulfonyl)ethyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-[(morpholin-4-yl)sulfonyl]ethyl]piperazine

2-[2-[(t-Butoxycarbonylamino)sulfonyl]ethyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-[(n-Butoxycarbonylamino)sulfonyl]ethyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(Ethoxycarbonylamino)sulfonyl]ethyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(Acetylamino)sulfonyl]ethyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-(Aminosulfonylmethyl)-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)sulfonylmethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(pyrrolidin-1-yl)sulfonylmethyl]piperazine

2-[(t-Butoxycarbonylamino)sulfonylmethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[(n-Butoxycarbonylamino)sulfonylmethyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(ethoxycarbonylamino)sulfonylmethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[ (Acetylamino) sulfonylmethyl]-4-[ (5-chloroindol-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

5 2-(Aminosulfonylmethyl)-4-[ (5-ethynylindol-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

4-[ (5-Ethynylindol-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[ (morpholin-4-yl) sulfonylmethyl]piperazine

10 4-[ (5-Ethynylindol-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]-2-[ (pyrrolidin-1-yl) sulfonylmethyl]piperazine

15 2-[ (t-Butoxycarbonylamino) sulfonylmethyl]-4-[ (5-ethynylindol-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[ (n-Butoxycarbonylamino) sulfonylmethyl]-4-[ (5-ethynylindol-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

20 2-[ (Ethoxycarbonylamino) sulfonylmethyl]-4-[ (5-ethynylindol-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[ (Acetylamino) sulfonylmethyl]-4-[ (5-ethynylindol-2-yl) sulfonyl]-1-[ (6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl) carbonyl]piperazine

2-[3-[(4H-5-Acetoxy-4-oxo)pyran-2-yl]propyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[3-[(4H-5-hydroxy-4-oxo)pyran-2-yl]propyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[3-[(4H-5-methoxy-4-oxo)pyran-2-yl]propyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

N-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetyl]-N-methylmethanesulfonamide

N-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetyl]benzenesulfonamide

N-[2-[4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-

yl]ethyl]trifluoromethanesulfonamide

N-[2-[4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]ethyl]-N-methyltrifluoromethanesulfonamide

N-[[4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazin-2-yl]acetyl]-N'-  
methanesulfonylhydrazine

2-[3-[(4H-5-Acetoxy-4-oxo)pyran-2-yl]propyl]-4-[(5-  
ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-

5 tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[3-[(4H-5-hydroxy-4-  
oxo)pyran-2-yl]propyl]-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[3-[(4H-5-methoxy-4-  
10 oxo)pyran-2-yl]propyl]-1-[(6-methyl-4,5,6,7-

tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

N-methyl-N-[[4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-  
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazin-2-yl]acetyl]methanesulfonamide

15 N-[[4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazin-2-yl]acetyl]benzenesulfonamide

N-[2-[4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

20 yl)carbonyl]piperazin-2-

yl]ethyl]trifluoromethanesulfonamide

N-[2-[4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-  
4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-

yl)carbonyl]piperazin-2-yl]ethyl]-N-

25 methyltrifluoromethanesulfonamide

N-[[4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazin-2-yl]acetyl]-N'-methanesulfonylhydrazine

5        4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10       4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15       4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)ethyl]piperazine

20       4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)ethyl]piperazine

25       4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)ethyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-(2-oxo-3H-1,2,3,5-oxathiadiazol-4-yl)ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl)ethyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(2,5-Dihydro-5-oxo-4H-1,2,4-thiadiazol-3-yl)ethyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[2-(2,5-Dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-4-[(5-ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[2-(2,5-dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

1-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(2-hydroxyethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N,N-Bis(2-hydroxyethyl)carbamoyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N,N-Bis(2-hydroxyethyl)carbamoyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(2-methoxyethyl)carbamoyl]methyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N,N-Bis(2-methoxyethyl)carbamoyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N,N-Bis(2-methoxyethyl)carbamoyl]methyl]-4-[(5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine



4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(2-hydroxyethyl)-  
N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[[N-(2-hydroxyethyl)-  
N-methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

2-[[N-Benzyl-N-(2-hydroxyethyl)carbamoyl)methyl]-4-[(5-  
chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 2-[[N-benzyl-N-(2-hydroxyethyl)carbamoyl)methyl]-4-[(5-  
chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 4-[(5-Chloroindol-2-yl)sulfonyl]-2-(2-cyanoethyl)-1-[(6-  
methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-cyanomethyl-N-  
methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20 4-[(5-Chloroindol-2-yl)sulfonyl]-2-[(N-cyanomethyl-N-  
methylcarbamoyl)methyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-  
tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-  
[(morpholin-4-yl)carbonyl]ethyl]piperazine

4-[(5-Chloroindol-2-yl)sulfonyl]-2-[2-(dimethylaminocarbonyl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

5 4-[(5-Chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-[(pyridin-1-yl)carbonyl]ethyl]piperazine

4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-[(morpholin-4-yl)carbonyl]ethyl]piperazine

10 4-[(5-Ethynylindol-2-yl)sulfonyl]-2-[2-(dimethylaminocarbonyl)ethyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

15 4-[(5-Ethynylindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[2-[(pyridin-1-yl)carbonyl]ethyl]piperazine

2-(3-Butynyl)-4-[(5-chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

20 2-(3-Butynyl)-4-[(5-chloroindol-2-yl)sulfonyl]-4-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

4-[(6-Chloro-3-hydroxybenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(6-Chloro-3-hydroxybenzo[b]thien-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

5 4-[(6-Chloro-3-hydroxybenzo[b]thien-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(6-Chloro-3-hydroxybenzo[b]thien-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

10 4-[(6-Chloro-3-hydroxybenzo[b]thien-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(2-cyanoethyl)piperazine

15 4-[(6-Chloro-3-hydroxybenzo[b]thien-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(3-Acetyl-6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-  
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

20 4-[(3-Acetyl-6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-  
 methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(3-Acetyl-6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-  
 methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(3-Acetyl-6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

5 4-[(3-Acetyl-6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(3-Acetyl-6-chlorobenzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

10 4-[(6-Chloro-3-(hydroxymethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

15 4-[(6-Chloro-3-(hydroxymethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

20 4-[(6-Chloro-3-(hydroxymethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

25 4-[(6-Chloro-3-(hydroxymethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(6-Chloro-3-(hydroxymethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

5 4-[(6-Chloro-3-(hydroxymethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

10 4-[(6-Chloro-3-(N,N-dimethylaminomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(6-Chloro-3-(N,N-dimethylaminomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

15 4-[(6-Chloro-3-(N,N-dimethylaminomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylemethyl)piperazine

20 4-[(6-Chloro-3-(N,N-dimethylaminomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylemethyl)piperazine

25 4-[(6-Chloro-3-(N,N-dimethylaminomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(6-Chloro-3-(N,N-dimethylaminomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

5 4-[(6-Chloro-3-(cyanomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

10 4-[(6-Chloro-3-(cyanomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

15 4-[(6-Chloro-3-(cyanomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(6-Chloro-3-(cyanomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

20 4-[(6-Chloro-3-(cyanomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

25 4-[(6-Chloro-3-(cyanomethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(6-Chloro-3-(carbamoylmethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

5 4-[(6-Chloro-3-(carbamoylmethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

10 4-[(6-Chloro-3-(carbamoylmethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

15 4-[(6-Chloro-3-(carbamoylmethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(6-Chloro-3-(carbamoylmethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

20 4-[(6-Chloro-3-(carbamoylmethyl)benzo[b]thien-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

25 4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

5 4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-1-[(6-hydroxymethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

1-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-4-[(6-hydroxymethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]piperazine

10 4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylemethyl)piperazine

4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylemethyl)piperazine

4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

20 4-[(5-Chloro-3-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(3-Acetyl-5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine



4-[(3-Acetyl-5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

5 4-[(3-Acetyl-5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(3-Acetyl-5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

10 4-[(3-Acetyl-5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

15 4-[(3-Acetyl-5-chloroindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(5-Chloro-3-(hydroxymethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

20 4-[(5-Chloro-3-(hydroxymethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(5-Chloro-3-(hydroxymethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(5-Chloro-3-(hydroxymethyl)indol-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

5 4-[(5-Chloro-3-(hydroxymethyl)indol-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(5-Chloro-3-(hydroxymethyl)indol-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(2-cyanoethyl)piperazine

10 4-[(5-Chloro-3-(N,N-dimethylaminomethyl)indol-2-  
 yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-  
 c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-  
 ylcarbonyl)methyl]piperazine

15 4-[(5-Chloro-3-(N,N-dimethylaminomethyl)indol-2-  
 yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
 c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-  
 ylcarbonyl)methyl]piperazine

20 4-[(5-Chloro-3-(N,N-dimethylaminomethyl)indol-2-  
 yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-  
 c]pyridin-2-yl)carbonyl]-2-(N,N-  
 dimethylcarbamoylmethyl)piperazine

25 4-[(5-Chloro-3-(N,N-dimethylaminomethyl)indol-2-  
 yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-  
 c]pyridin-2-yl)carbonyl]-2-(N,N-  
 dimethylcarbamoylmethyl)piperazine

4-[(5-Chloro-3-(N,N-dimethylaminomethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

5 4-[(5-Chloro-3-(N,N-dimethylaminomethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(5-Chloro-3-(cyanomethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

10 4-[(5-Chloro-3-(cyanomethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

15 4-[(5-Chloro-3-(cyanomethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(5-Chloro-3-(cyanomethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

20 4-[(5-Chloro-3-(cyanomethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(5-Chloro-3-(cyanomethyl)indol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(5-Chloro-3-(carbamoylmethyl)indol-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(5-Chloro-3-(carbamoylmethyl)indol-2-yl)sulfonyl]-1-  
 5 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-[(morpholin-4-ylcarbonyl)methyl]piperazine

4-[(5-Chloro-3-(carbamoylmethyl)indol-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

10 4-[(5-Chloro-3-(carbamoylmethyl)indol-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(N,N-dimethylcarbamoylmethyl)piperazine

4-[(5-Chloro-3-(carbamoylmethyl)indol-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-  
 15 yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(5-Chloro-3-(carbamoylmethyl)indol-2-yl)sulfonyl]-1-  
 [(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-  
 yl)carbonyl]-2-(2-cyanoethyl)piperazine

4-[(5-Chloro-1-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-  
 20 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [(morpholin-4-yl)carbonylmethyl]piperazine

4-[(5-Chloro-1-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-  
 4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-  
 [(morpholin-4-yl)carbonylmethyl]piperazine

4-[(5-Chloro-1-methoxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[(5-Chloro-1-methoxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[4-[(6-Chloro-1-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[4-[(6-Chloro-1-hydroxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[4-[(6-chloro-1-methoxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

4-[4-[(6-Chloro-1-methoxyindol-2-yl)sulfonyl]-1-[(6-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]pyridin-2-yl)carbonyl]-2-[(morpholin-4-yl)carbonylmethyl]piperazine

In the present invention, in addition to the above-exemplified compounds, salts thereof and solvates thereof can be mentioned as preferred examples.

The process for the preparation of the sulfonyl derivative of the present invention will next be described.

The sulfonyl derivative or salt thereof, or solvate thereof according to the present invention can be prepared by using general, conventionally-known chemical processes

in combination. Typical synthesis processes will be described subsequently.

Upon synthesis of the sulfonyl derivative of the present invention, when it is necessary to protect a substituent such as nitrogen atom, hydroxyl group or carboxyl group, it may be protected with an ordinary, conventionally-known protecting group which can be removed as needed. Such a protecting group can be removed at need by the synthesis process ordinarily employed in the organic chemistry which will be described below.

The starting materials necessary for the synthesis can be obtained by the synthesis process ordinarily employed in the organic chemistry and such a process will be described in Referential Examples. The starting materials for the sulfonyl derivative of the present invention can also be synthesized by the application of the process described in Referential Examples.

A description will next be made of a protecting group for the substituent such as nitrogen atom, hydroxyl group or carboxyl group and deprotection process thereof.

As a protecting group for the nitrogen atom in an amino or alkylamino group, ordinary acyl-type protecting groups are suited. Examples include alkanoyl groups such as acetyl, alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl and tertiary butoxy carbonyl, arylmethoxycarbonyl groups such as benzyloxycarbonyl, paramethoxyben-

zyloxycarbonyl and para- (ortho-)nitrobenzyloxycarbonyl groups, arylmethyl groups such as benzyl and triphenylmethyl and aroyl groups such as benzoyl. The removing process of such a protecting group differs with the chemical properties of the protecting group adopted. For example, the acyl-type protecting group such as alkanoyl, alkoxycarbonyl or aroyl can be removed by hydrolysis using an appropriate base such as alkali metal hydroxide, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide.

The substituted methoxycarbonyl type protecting group such as tertiary butoxycarbonyl or paramethoxybenzyloxycarbonyl can be removed by using an appropriate acid, for example, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. The arylmethoxycarbonyl group such as benzyloxycarbonyl, paramethoxybenzyloxycarbonyl or para- (ortho-)nitrobenzyloxycarbonyl, or the arylmethyl group such as benzyl can be removed by hydrogenolysis in the presence of a palladium-carbon catalyst. The benzyl group can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium, whereby conversion into a nitrogen-hydrogen bond can be effected. The triphenylmethyl group can be removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or

trifluoromethanesulfonic acid or combination thereof. It can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium or by hydrogenolysis in the presence of a palladium-carbon catalyst.

5        In addition to the above-described amino-protecting group, a phthaloyl type protecting group can be adopted for a primary amino group and it can be removed using hydrazine, dimethylaminopropylamine or the like. The amino group can also be protected with the nitrogen atom of in-  
10        dole, a phenylsulfonyl group, a toluenesulfonyl group, an acetyl group, a trifluoroacetyl group or the like and deprotection can be carried out by hydrolysis using a proper base such as sodium hydroxide, lithium hydroxide or potassium hydroxide.

15        As the protecting group suited for a hydroxyl group, there are acyl type and ether type ones. Examples of the acyl type protecting group include alkanoyl groups such as acetyl and aroyl groups such as benzoyl, while those of the ether type protecting group include arylmethyl groups such  
20        as benzyl, silyl ether groups such as tertiary butyl dimethylsilyl, methoxymethyl and tetrahydropyranyl. The removal of such a protecting group differs with the chemical properties of the protecting group adopted. For example, the acyl group such as alkanoyl or aroyl can be removed by  
25        the hydrolysis using an appropriate base such as an alkali metal hydroxide, for example, lithium hydroxide, sodium hy-



dioxide or potassium hydroxide. The arylmethyl type protecting group can be removed by the hydrogenolysis using a palladium-carbon catalyst. The silyl group such as tertiary butyl dimethylsilyl can be removed using a salt of hydrofluoride such as tetrabutyl ammonium fluoride. The methoxymethyl or tetrahydropyranyl group can be removed using acetic acid, hydrochloric acid or the like. The hydroxyl group substituted for an aryl group can be protected with a methyl group and deprotection can be carried out using a Lewis acid such as aluminum chloride, boron trifluoride or phosphorus tribromide, trimethylsilyl iodide or hydrogen bromide.

A carboxyl group can be protected by the esterification of it. A methyl or ethyl ester can be deprotected by the hydrolysis using an appropriate base such as alkali metal hydroxide, e.g., lithium hydroxide, sodium hydroxide or potassium hydroxide, while from a tertiary butyl ester, the tertiary butyl group can be removed by treating with trifluoroacetic acid or hydrochloric acid. From an arylmethyl type ester such as benzyl, the arylmethyl group can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst.

As the protecting group for acetylene, an alkylsilyl group such as trimethylsilyl, tertiary-butyldimethylsilyl or tertiary-butyldiphenylsilyl can be employed and deprotection can be carried out using a proper base, for exam-

ple, an alkali metal hydroxide such as sodium hydroxide, lithium hydroxide or potassium hydroxide or a salt of hydrofluoride such as tetrabutylammonium fluoride or pyridine hydrofluoride.

5 [Preparation Process-1]

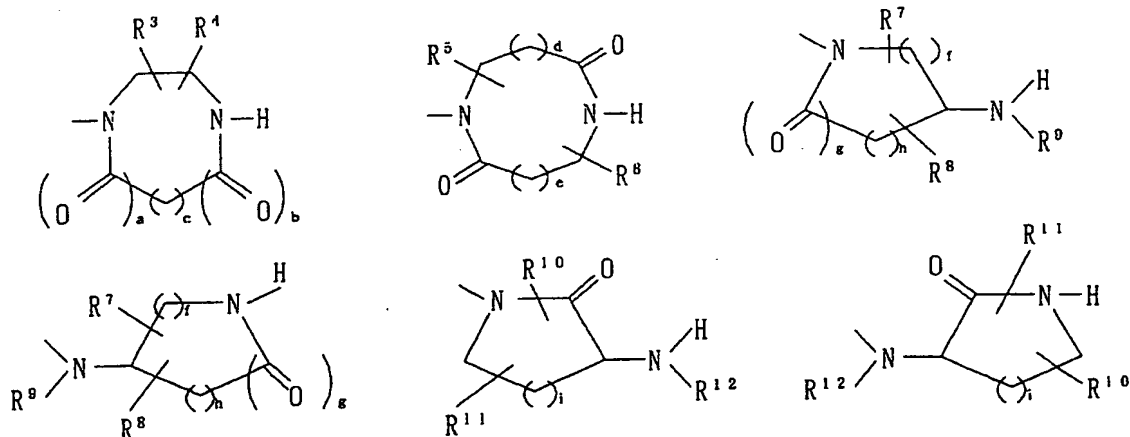
A process for preparing a sulfonyl derivative represented by the following formula (I):



10 [wherein  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  and  $T^1$  have the same meanings as described above], which comprises sulfonylating the nitrogen atom of  $Q^{3a}$  of the compound represented by the following formula (Ia):



15 [wherein  $Q^1$ ,  $Q^2$  and  $T^1$  have the same meanings as described above and  $Q^{3a}$  represents any one of the groups represented by the following formulas:



(in which  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$ ,  $R^{11}$ ,  $R^{12}$ , a, b, c, d, e, f, g, h and i have the same meanings as described

above)] with a sulfonic acid halide represented by the following formula (IIa):



[wherein  $\text{Q}^{\text{A}}$  has the same meaning as described above and

5 Halo represents a halogen atom such as chlorine, bromine or iodine].

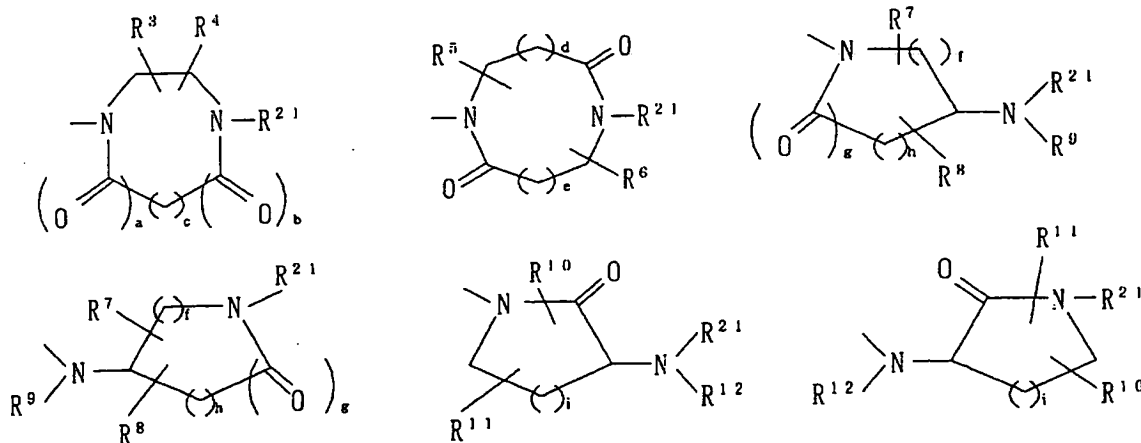
<Synthesis of the compound of the formula (Ia)>

The compound of the formula (Ia) can be synthesized by a series of procedures in accordance with the known technique.

For example, a compound of the following formula (Ib):



[wherein  $\text{Q}^1$ ,  $\text{Q}^2$  and  $\text{T}^1$  have the same meanings as described above and  $\text{Q}^{3\text{b}}$  represents any one of the following groups:

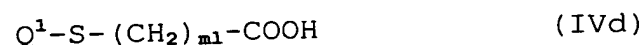
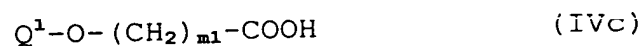
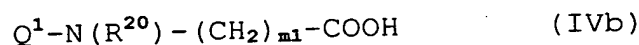


(wherein  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{10}$ ,  $\text{R}^{11}$ ,  $\text{R}^{12}$ ,  $a$ ,  $b$ ,  $c$ ,  $d$ ,  $e$ ,  $f$ ,  $g$ ,  $h$  and  $i$  have the same meanings as described above and  $\text{R}^{21}$  represents an ordinary nitrogen protecting group such as tertiary butoxycarbonyl, benzyloxycarbonyl,

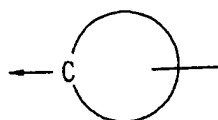
paramethoxybenzyloxycarbonyl, paranitrobenzyloxycarbonyl or benzyl)] can be synthesized by acylating the nitrogen atom of the compound - which can be synthesized in a conventionally known manner or by application thereof and is represented by the following formula (IIIa):



(wherein  $Q^{3b}$  has the same meaning as described above)- to which the hydrogen atom of  $Q^{3b}$  has been bonded, with a carboxylic acid in an activated form represented by any one of the following formulas (Iva) to (Ivd):

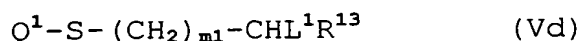
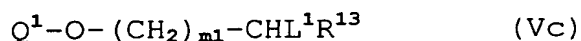
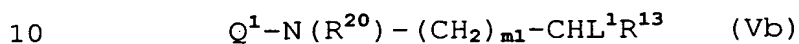


[wherein  $Q^1$  has the same meaning as described above,  $R^{20}$  represents an ordinary nitrogen protecting group such as linear or branched alkylkylene, tertiary butoxycarbonyl, benzyloxycarbonyl, paramethoxybenzyloxycarbonyl, paranitrobenzyloxycarbonyl or benzyl,  $Q^{2b}$  represents a single bond, a linear or branched  $C_{1-6}$  alkylene, a linear or branched  $C_{2-6}$  alkenylene, a linear or branched  $C_{2-6}$  alkynylene or a group of the following formula:



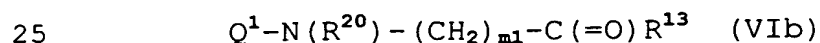
(which has the same meaning as described above) and  $m_1$  stands for an integer of 1 to 6].

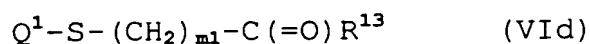
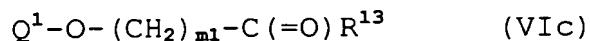
When the nitrogen atom of  $Q^{3b}$  of the compound represented by the formula (IIIa) forms an amide bond, the compound of the formula (Ib) can be synthesized by alkylating the nitrogen atom of  $Q^{3b}$  of the compound represented by the formula (IIIa) with any one of the compounds represented by the following formulas (Va) to (Vd):



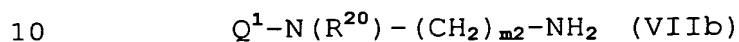
[wherein  $Q^1$ ,  $Q^{2b}$ ,  $R^{13}$ ,  $R^{20}$  and  $m_1$  have the same meanings as described above, and  $L^1$  represents an eliminating group frequently used in the organic chemistry, such as chlorine, bromine, iodine, methylsulfonyloxy or paratoluenesulfonyloxy].

When the nitrogen atom of  $Q^{3b}$  of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can be prepared by reductive alkylation, that is, by forming the corresponding imine with a carbonyl compound represented by any one of the following formulas (VIa) to (VIId):

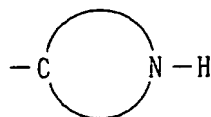




[wherein  $Q^1$ ,  $Q^{2b}$ ,  $R^{13}$ ,  $R^{20}$  and  $m1$  have the same meanings as described above], followed by reduction; by reacting the compound of the formula (IIIa) with a reagent such as phos-  
 5 gene, triphosgene or 1,1'-carbonyldiimidazole and a compound containing a primary amine represented by any one of the following formulas (VIIa) to (VIId) or formula (VIIe):



wherein  $Q^1$ ,  $Q^{2b}$  and  $R^{20}$  have the same meanings as described  
 15 above and  $m2$  stands for an integer of 2 to 6 and a group of the following formula:



represents a 5- or 6-membered heterocyclic group which may have a substituent)], thereby forming the corresponding  
 20 urea derivative; or by reacting the amine of the formula (IIIa) with an isocyanate derivative or an isocyanate prepared from a carboxylic acid represented by any one of the

formulas (IVa) to (IVd).

When in the structure of  $Q^1$  of the compound represented by the formula (Ib), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, coupling reaction can be effected with a boric-acid-substituted aryl compound in the presence of a transition metal catalyst.

When in the structure of  $Q^1$  of the compound represented by the formula (Ib), an alkenyl group or boric-acid-substituted alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group in the presence of a transition metal catalyst.

When in the structure of  $Q^1$  of the compound represented by the formula (Ib), a boric-acid-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl compound or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl compound. When in the structure of  $Q^1$  of the compound represented by the formula (Ib), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group is contained, it can be subjected to coupling reaction with an alkenyl compound in the presence of a transition metal catalyst, whereby the compound of the

formula (Ib) can be obtained. If the nitrogen atom of  $Q^{3b}$  of the compound (Ib) so obtained has been protected, the compound of the formula (Ia) can be obtained by deprotection as needed.

5        Examples of the carboxylic acids of the following formulas (IVa) to (IVd) in an activated form include acid mixed acid anhydrides available by reacting any one of the carboxylic acids of the formulas (IVa) to (IVd) with a chloroformate ester such as isobutyl chloroformate; acid  
10        halides such as acyl chloride prepared using an acid halide such thionyl chloride; active esters obtained by reacting with a phenol such as paranitrophenol or pentafluorophenyltrifluoroacetate; active esters obtained by reacting with  
15        N-hydroxybenztriazole or N-hydroxysuccinimide; reaction products with 1-benztriazolyloxy-(pyrrolidino)-phosphonium hexafluorophosphite, N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride which is usually employed for the peptide synthesis of  
20        amino acid, reaction products with diethyl cyanophosphonate (salting-in method) and reaction products with triphenylphosphine and 2,2'-dipyridylsulfide (Mukaiyama's method).

      The resulting carboxylic acid in an activated form is then reacted with the compound of the formula (IIIa) or salt thereof generally in the presence of an appropriate  
25        base in an inert solvent at  $-78^{\circ}\text{C}$  to  $150^{\circ}\text{C}$ , whereby the compound of the formula (Ib) can be obtained.



Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium methoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic base of bisilylamine compounds such as lithium  
 5 bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

Examples of the inert solvent include alkyl halide  
 15 solvents such as dichloromethane, chloroform and carbon tetrachloride; ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane; aromatic solvents such as benzene and toluene; and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one.  
 20 In addition to them, sulfoxide solvents such as dimethylsulfoxide and sulfolane and ketone solvents such as acetone and methyl ethyl ketone can be used if they are suited.

When the nitrogen atom of  $Q^{3b}$  of the compound represented by the formula (IIIa) forms an amide bond, the alkylation of the nitrogen atom is carried out by reacting the  
 25

compound (IIIa) with the compound represented by any one of the formulas (Va) to (Vd) in the presence of an appropriate base in an inert solvent at -78 to 150°C, whereby the compound of the formula (Ib) can be obtained. Specific examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic base of bissilylamine compounds such as lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU).

Examples of the inert solvent include ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane and amide solvents such as N,N-dimethylformamide.

When the nitrogen atom of Q<sup>3b</sup> of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can be obtained by reacting the compound of the formula (IIIa) with the carbonyl compound of any one of the formulas (VIa) to (VIId) to form the corresponding imine, generally in an inert solvent, optionally in the presence of an organic acid such as acetic acid, a mineral acid such as hydrochloric acid or a Lewis acid such as aluminum chloride at -20 to 150°C; and then hydrogenating the resulting imine in an in-

ert solvent in the presence of a boron hydride reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride or a catalytic hydrogenation catalyst such as palladium-carbon catalyst at 10 to 110°C.

Preferred examples of the inert solvent include carbon halides such as dichloromethane, chloroform and carbon tetrachloride, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane, benzene solvents such as toluene and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one.

When the nitrogen atom of Q<sup>3b</sup> of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the reaction product of the compound of any one of the formulas (VIIa) to (VIId) containing a primary amine or the compound of the formula (VIIe) containing a secondary amine with a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole can be acted on the compound of the formula (IIIa) to introduce it to the corresponding urea derivative. The derivative can be synthesized by reacting the primary amine compound of any one of the formulas (VIIa) to (VIId) or the secondary amine compound of the formula (VIIe), a reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole and the compound of the formula (IIIa) successively in this order, if necessary in the presence of a base, in an inert solvent.

Examples of the inert solvent include halogen solvents such as dichloromethane, chloroform and carbon tetrachloride; ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane; benzene solvents such as toluene; and amide solvents such as N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. Among them, dichloromethane, tetrahydrofuran and toluene are preferred.

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is effected within a temperature range of from -70°C to 110°C.

When the nitrogen atom of  $Q^{3b}$  of the compound represented by the formula (IIIa) exists as a primary or secondary amine, the compound of the formula (Ib) can also be obtained by reacting the compound of the formula (IIIa) with an isocyanate derivative in an inert solvent at -20 to 100°C.

The isocyanate derivative can be synthesized by converting the carboxylic acid of the formula (IVa) into the corresponding acid halide by using an acid halide such as thionyl chloride or oxalyl chloride in an inert solvent

such as tetrahydrofuran, chloroform or toluene at -20 to 110°C, reacting the resulting acid halide with sodium azide in an inert solvent such as tetrahydrofuran, chloroform or toluene at a temperature range of from 0 to 80°C, and then heating the reaction mixture at 20 to 100°C; by reacting the carboxylic acid of the formula (IVa) with a chloroformate such as isobutyl chloroformate in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C to obtain the corresponding mixed acid anhydride, reacting the mixed acid anhydride with sodium azide within a temperature range of from 0 to 80°C and then heating the reaction mixture at 20 to 100°C; or by introducing the carboxylic acid of the formula (IVa) into the corresponding hydrazide through an ester in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C, reacting the hydrazide with nitric acid or alkyl ester thereof to convert it into the corresponding acyl azide and then heating the resulting acyl azide in a solvent such as chloroform, dichloroethane, toluene, xylene or N,N-dimethylformamide at 20 to 150°C.

The compound of the formula (Ib) can also be prepared by reacting the carboxylic acid of the formula (IVa) with diphenylphosphoryl azide in the presence of a base such as triethylamine, in an inert solvent such as chloroform, tetrahydrofuran, toluene or N,N-dimethylformamide at a temperature range of 10 to 140°C and then reacting the reac-

tion mixture with the amine of the formula (IIIa).

When in the structure of  $Q^1$  of the compound represented by the formula (Ib), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, the compound can be subjected to coupling reaction with a boric-acid-substituted aryl derivative by using a transition metal catalyst such as

tetrakis(triphenylphosphine)palladium (0), in a two-phase solvent such as benzene-water or toluene-water, amide solvent such as N,N-dimethylformamide or ether solvent such as tetrahydrofuran or dimethoxyethane, optionally in the presence of as sodium carbonate, sodium hydroxide, calcium hydroxide, barium hydroxide, potassium phosphate or cesium carbonate at a temperature range of 20 to 150°C for 0.5 to 120 hours.

When an alkenyl group or boric-acid-substituted alkenyl group is contained in the structure of  $Q^1$  of the compound represented by the formula (Ib), coupling reaction of the compound with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group can be effected using a transition metal catalyst such as palladium acetate, in the presence of an appropriate base or cesium fluoride, in an amide solvent such as N,N-dimethylformamide, at a temperature range of 20 to 150°C for 0.5 to 120 hours. When a boric-acid-substituted aryl group is contained in the structure

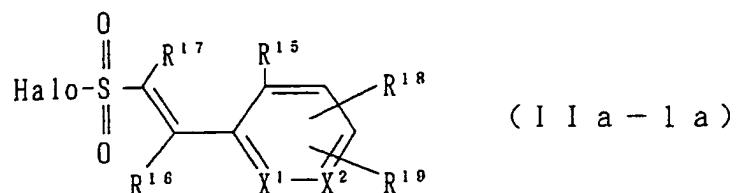
of  $Q^1$  of the compound represented by the formula (Ib), coupling reaction of the compound with a halogen- or trifluoromethanesulfonyloxy-substituted aryl derivative or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl derivative can be effected. When a halogen- or trifluoromethanesulfonyloxy-substituted aryl group is contained in the structure of  $Q^1$  of the compound represented by the formula (Ib), coupling reaction of the compound with an alkenyl compound can be effected using a transition metal catalyst, whereby the compound of the formula (Ib) can be obtained.

If the nitrogen atom of  $Q^{3b}$  of the resulting compound represented by the formula (Ib) has been protected, the compound of the formula (Ia) can be obtained by deprotection as needed.

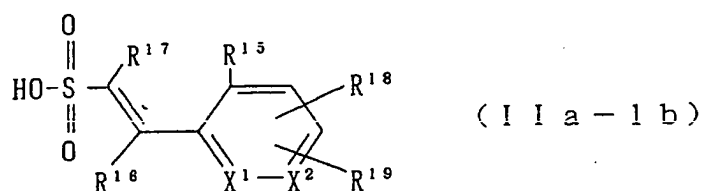
<Synthesis of the compound represented by the formula (IIa)>

The sulfonic acid halide of the formula (IIa) can be synthesized in a known matter or by application thereof. The ordinarily employed synthesis process will be described below.

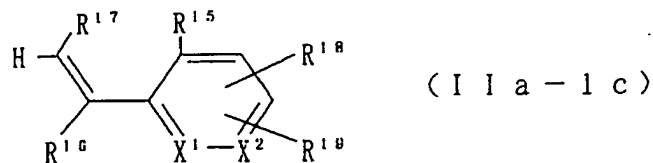
Among the sulfonic acid halides represented by the formula (IIa), a sulfonic acid halide represented by the following formula (IIa-1a):



[wherein  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $X^1$ ,  $X^2$  and Halo have the same meanings as described above] can be synthesized by any one of the various processes reported to date (The Chemistry of Sulfonic Acids Esters and their Derivatives, Edited by S. Patai and Z. Rappoport, 1991, John Wiley & Sons Ltd.), for example, halogenation of a sulfonic acid of the following formula (IIa-1b):



[wherein  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $X^1$  and  $X^2$  have the same meanings as described above] or chlorosulfonylation of the unsaturated bond represented by the following formula (IIa-1c):



[wherein  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $X^1$  and  $X^2$  have the same meanings as described above].

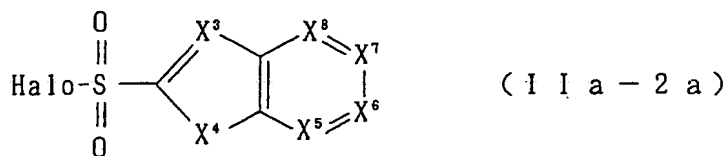
For example, the sulfonic acid halide of the formula (IIa-1a) can be obtained by reacting the sulfonic acid of



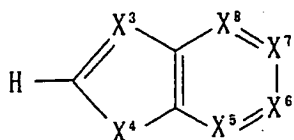
the formula (IIa-1b) with a thionyl halide in the presence of N,N-dimethylformamide at 0 to 150°C for 0.5 to 24 hours. At this time, the reaction system may be diluted with an inert solvent such as dichloromethane, chloroform, carbon tetrachloride, N-methylpyrrolidin-2-one, dimethylsulfoxide or sulfolane.

The sulfonic acid halide of the formula (IIa-1a) can be obtained by reacting the unsaturated-bond-containing compound of the formula (IIa-1c) with a thionyl halide or chlorosulfonic acid in an inert solvent such as N,N-dimethylformamide at 0 to 150°C for 0.5 to 24 hours.

Among the sulfonic acid halides represented by the formula (IIa), a sulfonic acid halide represented by the following formula (IIa-2a):



[wherein X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>, X<sup>6</sup>, X<sup>7</sup>, X<sup>8</sup> and Halo have the same meanings as described above] can be obtained by the processes so far reported (Japanese Patent Application Laid-Open No. Sho 60-204760, Japanese Patent Application Laid-Open No. Sho 62-116575, Japanese Patent Application Laid-Open No. Hei 4-128266) or by application thereof, for example, by reacting the fused heterocycle represented by the following formula (IIa-2b):



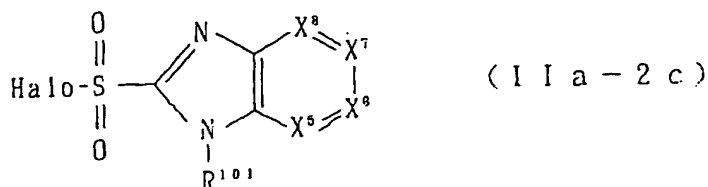
(IIa-2b)

[wherein  $X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$ ,  $X^7$  and  $X^8$  have the same meanings as described above] with a base and then sulfur dioxide and then reacting the reaction mixture with a halogenating agent.

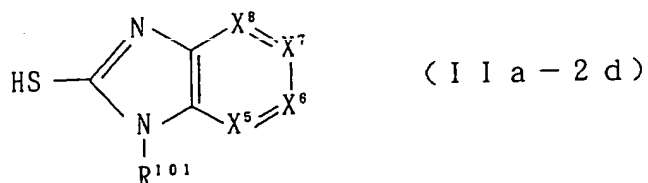
The compound of the formula (IIa-2a) is obtained, for example, by reacting the fused heterocycle of the formula (IIa-2b) with an appropriate base in an ether-type inert solvent at  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ , reacting the reaction mixture with sulfur dioxide at  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ , and then reacting with a halogenating agent in an alkyl halide type inert solvent at  $-50^\circ\text{C}$  to  $50^\circ\text{C}$ . Specific examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium botoxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic base of bisssilylamine compounds such as lithium bis(trimethylsilyl)amide. Examples of the ether-type inert solvent include diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and dioxane. Preferred examples of the halogenating agent include chlorine, bromine, phosphorus pentachloride, thionyl chloride, N-chlorosuccinimide and N-bromosuccinimide, while those of the alkyl halide type in-

ert solvent include dichloromethane, chloroform and tetrachloroethane.

Among the compounds represented by the formula (IIa-2a), the corresponding sulfonyl chloride of the compound represented by the following formula (IIa-2c):



[wherein  $R^{101}$ ,  $X^5$ ,  $X^6$ ,  $X^7$ ,  $X^8$  and Halo have the same meanings as described above] can be obtained by reacting the compound of the following formula (IIa-2d):



[wherein  $R^{101}$ ,  $X^5$ ,  $X^6$ ,  $X^7$  and  $X^8$  have the same meanings as described above] with halogen such as a chlorine gas at 0 to 30°C for 10 minutes to 6 hours in water or a mixed solvent of water with an organic carboxylic acid such as acetic acid.

The reaction between the compound of the formula (IIa-2d) and halogen is carried out at 0 to 20°C usually in water or a 10 to 90% aqueous solution of acetic acid if necessary in the presence of a Lewis acid such as ferric chloride as a catalyst.

<Reaction of a compound of the formula (Ia) with a compound of the formula (IIa)>

The compound of the formula (I) can be obtained generally by reacting the compound of the formula (Ia), which  
5 has been synthesized by the above-described process or the like, with the sulfonic acid halide of the formula (IIa) which has been synthesized by the above-described process or the like, in the presence of an appropriate base, in an inert solvent at -78 to 150°C.

10 The resulting compound of the formula (I) can be subjected to deprotection or chemical conversion of a substituent as needed.

Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium methoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium  
15 such as lithium diisopropylamide; organometallic base of bis(silyl)amine compounds such as lithium  
20 bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine  
25 and diazabicyclo[5.4.0]undec-7-ene (DBU).

Examples of the inert solvent include dichloromethane,

chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane and mixed solvents thereof.

5 [Preparation Process-1-(1)]

When the nitrogen atom of  $Q^{3a}$  of the compound represented by the formula (Ia), which is to be sulfonylated, exists as a primary or secondary amine, preferred examples of the base include carbonates and hydroxides of an alkali  
10 metal or an alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) and usable examples of the solvent include, in addition to inert solvents, water, alcohol solvents such as ethanol and butanol and ester solvents such as ethyl acetate.

15 [Preparation Process-1-(2)]

20 When the nitrogen atom of  $Q^{3a}$  of the compound represented by the formula (Ia), which is to be sulfonylated, forms an amide group, preferred examples of the base include alkoxides and hydrides of an alkali metal or an alkaline earth metal such as sodium ethoxide, potassium  
25 butoxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-

butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic base of bisilylamine compounds such as lithium bis(trimethylsilyl)amide; and organic bases such as diazabicyclo[5.4.0]undec-7-ene (DBU).

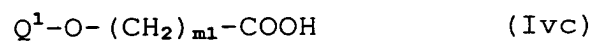
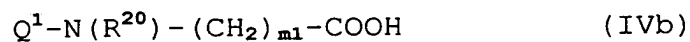
5 Examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane, dioxane and N,N-dimethylformamide.

[Preparation Process-2]

A process for preparing the sulfonyl derivative (I) by acylating the nitrogen atom of  $Q^{3a}$  of the compound represented  
10 by the formula (VIIIa):



[wherein  $Q^{3a}$  and  $Q^A$  have the same meanings as described above] with any one of the carboxylic acids represented by the formulas (IVa) to (IVd):

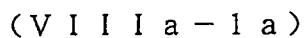


[wherein  $Q^1$ ,  $Q^2$ ,  $Q^{2b}$ ,  $R^{20}$  and  $m1$  have the same meanings as  
20 described above] or the activated form thereof which are available by the process reported to far or the chemically usual process.

The compound represented by the formula (VIIIa) can be synthesized in various processes. Some of them will next  
25 be described.

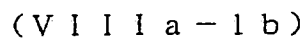
<Synthesizing process of a compound represented by the formula (VIIIa-1a)>

5

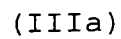


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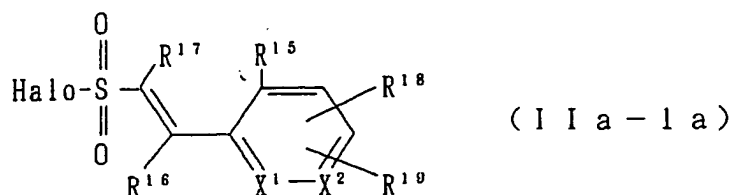
The compound of the following formula (VIIIa-1b):



15



[wherein Q<sup>3b</sup> has the same meaning as described above] with a compound represented by the following formula (IIa-1a):



[wherein  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $X^1$ ,  $X^2$  and Halo have the same meanings as described above] in the presence of an appropriate base in an inert solvent at  $-78$  to  $150^\circ\text{C}$ .

5           Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium botoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride;  
 10           organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic base of bissilylamine compounds such as lithium  
 15           bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

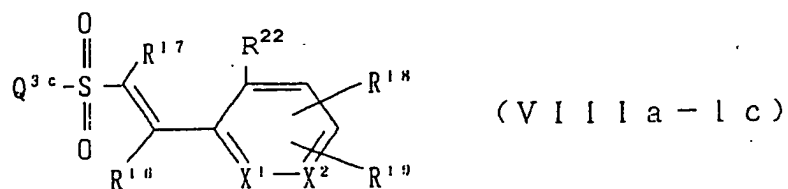
          Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-  
 20           dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide, sulfolane and acetone.

          If the nitrogen atom of  $Q^{3b}$  of the resulting compound



represented by the formula (VIIIa-1b) has been protected, the compound of the formula (VIIIa-1a) can be obtained by deprotection as needed.

The compound of the formula (VIIIa-1a) can be obtained by removing, in an appropriate manner, the protecting group of the nitrogen atom from the compound represented by the following formula (VIIIa-1c):



[wherein  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $X^1$  and  $X^2$  have the same mean-

ings as described above,  $R^{22}$  represents

a hydrogen atom,

an alkyl group,

a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

a hydroxyalkyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

an alkoxyl group,

an alkoxyalkyl group,

a dialkoxyalkyl group,

a dialkylamino group,

a monoalkylamino group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

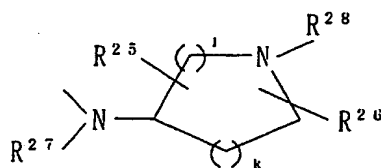
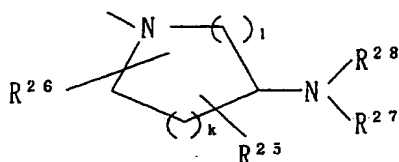
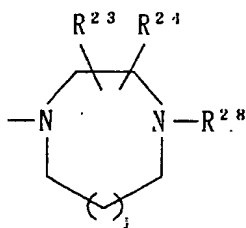
a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

5 a dialkylaminoalkyloxy group,

a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonylalkyloxy group or the like; and  $Q^{3c}$  represents any one of the following groups:



10

(wherein when the carbon atom to which  $R^{23}$ ,  $R^{24}$ ,  $R^{25}$  or  $R^{26}$  has been bonded is not adjacent to the nitrogen atom,  $R^{23}$ ,  $R^{24}$ ,  $R^{25}$  and  $R^{26}$  each independently represents:

a hydrogen atom,

15 an alkyl group,

a hydroxyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

a hydroxyalkyl group protected with a methoxymethyl, tetrahydropyranyl or the like group,

an alkoxyl group,

an alkoxyalkyl group,

a dialkoxyalkyl group,

a dialkylamino group,

5 a monoalkylamino group in which the amino moiety has been protected with a tertiary butoxycarbonyl group,

a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

10 a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

a dialkylaminoalkyloxy group, or the like.

$R^{23}$  and  $R^{24}$ , as well as  $R^{25}$  and  $R^{26}$ , may be coupled together to form a saturated or unsaturated 5- to 7-membered  
15 cyclic hydrocarbon group which may have a substituent or a saturated or unsaturated 5- to 7-membered heterocyclic group which may have a substituent.

$R^{27}$  represents:

an alkyl group,

20 a hydroxyalkyl group having the hydroxyl group protected,

a hydroxyalkylcarbonyl group having the hydroxyl group protected,

a hydroxyalkylsulfonyl having the hydroxyl group protected,  
25 tected,

an alkoxyalkyl group,

an alkoxyalkylcarbonyl group,  
 an alkoxyalkylsulfonyl group,  
 an alkylcarbonyl group,  
 an alkylcarbonylalkyl group,  
 5 an alkylsulfonyl group,  
 an alkylsulfonylalkyl group,  
 an alkoxy carbonyl group,  
 an alkoxy carbonylalkyl group,  
 an alkoxy carbonylalkylcarbonyl group,  
 10 an alkoxy carbonylalkylsulfonyl group,  
 a dialkylaminoalkyl group,  
 a monoalkylaminoalkyl group having the amino group  
 protected with a tertiary butoxycarbonyl group,  
 a dialkylaminocarbonyl group,  
 15 a dialkylaminocarbonylalkyl group, or the like.

$R^{25}$  and  $R^{27}$ , or  $R^{26}$  and  $R^{27}$  may be coupled together to  
 form a saturated or unsaturated 5- to 7-membered heterocyclic  
 group which may have a substituent.

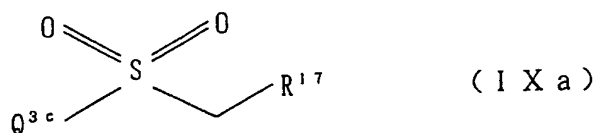
$R^{28}$  represents a tertiary butoxycarbonyl, benzyl or  
 20 triphenylmethyl group which means a protecting group of the  
 nitrogen atom, j and k each independently represents an integer  
 of 0 or 1 and l stands for an integer of 1 to 3 with  
 the proviso that the sum of k and l stands for an integer  
 of 1 to 4.))

25 The compound represented by the formula (VIIIa-1c) can  
 be obtained by reacting an amino compound which is avail-

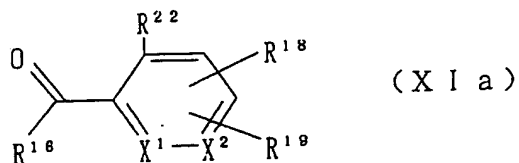
able by the known process or application thereof and is represented by the following formula (IIIb):



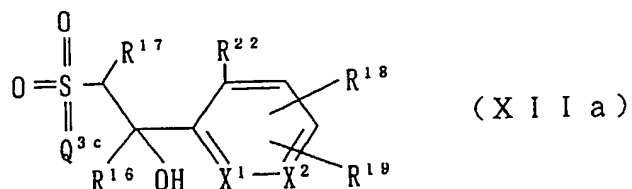
[wherein  $Q^{3c}$  has the same meaning as described above] with an alkylsulfonic acid halide in the presence of an appropriate base; reacting the resulting sulfonamide represented by the following formula (IXa):



[wherein  $R^{17}$  and  $Q^{3c}$  have the same meanings as described above] with a carbonyl compound represented by the following formula (XIa):



[wherein  $R^{16}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{22}$ ,  $X^1$  and  $X^2$  have the same meanings as described above] in an inert solvent in the presence of an appropriate base to obtain the corresponding alcohol product represented by the following formula (XIIa):



[wherein  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{22}$ ,  $Q^{3c}$ ,  $X^1$  and  $X^2$  have the same meanings as described above]; converting the alcohol moiety

of the alcohol product (XIIa) into a methanesulfonyloxy group or the like in the presence of an appropriate base, or converting the alcohol moiety into a halogen atom by using a phosphorus halide or triphenylphosphine/carbon tetra-  
5 halide, thereby forming an eliminating group; and then eliminating methanesulfonic acid or hydrogen halide in the presence of an appropriate base.

The sulfonamide compound of the formula (IXa) can be obtained by reacting the amino compound of the formula  
10 (IIIb), which is available in a known process or by application thereof, with an alkylsulfonic halide which may have a substituent, in the presence of an appropriate base, in an inert solvent at -78 to 150°C.

Examples of the base include carbonates of an alkali  
15 metal or alkaline earth metal, such as sodium carbonate and potassium carbonate and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

20 Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidin-2-one. Dimethylsulfoxide, sulfolane, acetone or the like can be  
25 used, though depending on the kind of the base employed.

The alcohol compound of the formula (XIIa) can be ob-

tained by reacting the sulfonamide of the formula (IXa) with a carbonyl compound of the formula (XIa) in the presence of an appropriate base in an inert solvent at -78 to 110°C.

5           Examples of the base include hydrides of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium methoxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium  
10   diisopropylamide; organometallic base of bisilylamine compounds such as lithium bis(trimethylsilyl)amide. Examples of the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane and dioxane.

          The compound of the formula (VIIIa-1c) can be obtained  
15   by treating the hydroxyl group of the alcohol product of the formula (XIIa) with a phosphorus halide such as phosphorus pentachloride or a triphenylphosphine-halogen complex such as triphenylphosphine dibromide at -20 to 110°C, if necessary in the presence of an appropriate base, for  
20   example, the carbonate of an alkali metal or alkaline earth metal, such as sodium carbonate or potassium carbonate, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo[5.4.0]undec-7-ene  
25   (DBU), in a solvent such as dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane,

dioxane, toluene or N,N-dimethylformamide, thereby obtaining the corresponding halide, and then eliminating the hydrogen halide from the resulting halide under basic conditions, for example, by treating at -78 to 150°C with a carbonate, alkoxide, hydroxide or hydride of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, an organometallic base compound typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide, an organometallic base of bis(trimethylsilyl)amine compound such as lithium bis(trimethylsilyl)amide, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

The compound of the formula (VIIIa-1c) can also be obtained by treating the hydroxyl group of the alcohol product represented by the formula (XIIa) with an alkyl- or arylsulfonic acid chloride such as methanesulfonic acid chloride in the presence of an appropriate base, for example, a carbonate of an alkali metal or alkaline earth metal



such as sodium carbonate or potassium carbonate or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo[5.4.0]undec-7-ene (DBU), in a solvent such as dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene or N,N-dimethylformamide at -20 to 110°C to obtain the corresponding alkyl- or arylsulfonate derivative; and then eliminating the alkyl- or arylsulfonic acid from the resulting alkyl- or arylsulfonate derivative under basic conditions.

Described specifically, the compound of the formula (VIIIa-1c) can be obtained by treating the resulting alkyl- or arylsulfonate derivative at -78 to 150°C in the presence of a carbonate, alkoxide, hydroxide or hydride of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, an organometallic base compound typified by alkyl lithium such as n-butyl lithium and dialkylamino-lithium such as lithium diisopropylamide, an organometallic base of bissilylamine compound such as lithium bis(trimethylsilyl)amide, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine or diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane,

chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulfoxide.

5       The compound of the formula (VIIIa-1c) can also be obtained by treating the sulfonamide of the formula (IXa) with a silyl halide such as trimethylsilyl chloride in the presence of an appropriate base in an inert solvent to convert it to the corresponding silyl compound, reacting the  
10       resulting silyl compound with a carbonyl compound of the formula (XIa) in the presence of a base in an inert solvent and then treating the reaction product under acidic to basic aqueous conditions (Peterson's reaction).

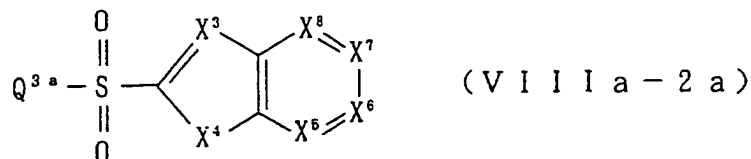
      Described specifically, the compound of the formula  
15       (VIIIa-1c) can be obtained by treating the sulfonamide of the formula (IXa) with an alkylsilyl chloride such as trimethylsilyl chloride at -78 to 110°C in the presence of an alkoxide or hydride of an alkali metal or alkaline earth metal such as sodium ethoxide, potassium butoxide, sodium  
20       hydride or potassium hydride, an organometallic base compound typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide, or an organometallic base of bissilylamine compound such as lithium bis(trimethylsilyl)amide in a solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane, to convert it to  
25       the corresponding silyl compound, condensing with the car-

bonyl compound of the formula (XIa) under the same conditions and then treating the condensate under acidic to basic aqueous conditions.

The protecting group of the nitrogen atom of the compound represented by the formula (VIIIa-1c) can be removed by the ordinarily employed process. Described specifically, when the protecting group is a tertiary butoxycarbonyl group, it can be removed by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. It can also be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIIIa-1c) can be obtained.

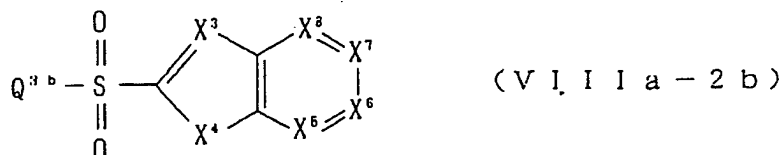
<Synthesis of the compound represented by the formula (VIIIa-2a)>

Among the compounds represented by the formula (VIIIa), the compound of the formula (VIIIa-2a):



[wherein  $\text{X}^3$ ,  $\text{X}^4$ ,  $\text{X}^5$ ,  $\text{X}^6$ ,  $\text{X}^7$ ,  $\text{X}^8$  and  $\text{Q}^{3a}$  have the same meanings as described above] can be synthesized by the following process.

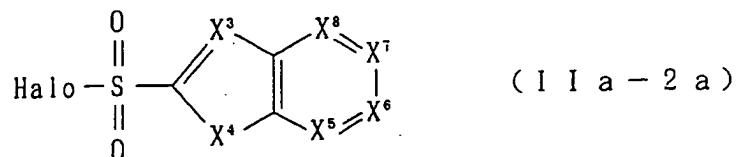
5 Described specifically, the compound of the following formula (VIIIa-2b):



[wherein  $\text{X}^3$ ,  $\text{X}^4$ ,  $\text{X}^5$ ,  $\text{X}^6$ ,  $\text{X}^7$ ,  $\text{X}^8$  and  $\text{Q}^{3b}$  have the same meanings as described above] can be obtained by sulfonylating the nitrogen atom of the primary or secondary amine or amide of the compound of the formula (IIIa):



[wherein  $\text{Q}^{3b}$  has the same meaning as described above] with a sulfonic acid halide represented by the following formula (IIa-2a):



[wherein  $\text{X}^3$ ,  $\text{X}^4$ ,  $\text{X}^5$ ,  $\text{X}^6$ ,  $\text{X}^7$ ,  $\text{X}^8$  and Halo have the same meanings as described above] in the presence of an appropriate base in an inert solvent at  $-78$  to  $150^\circ\text{C}$ .

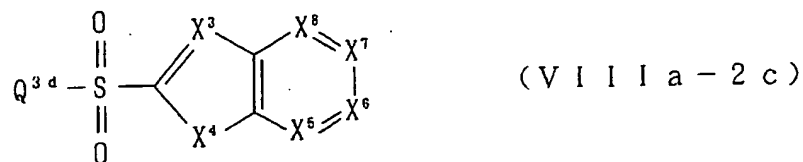
Specific examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic base of bissilylamine compounds such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide, sulfolane and acetone.

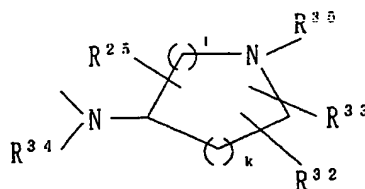
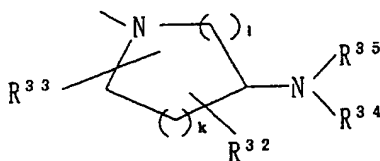
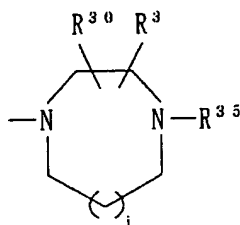
When the nitrogen atom of  $Q^{3b}$  of the resulting compound represented by the formula (VIIIa-2b) has been protected, the compound of the formula (VIIIa-2a) can be obtained by carrying out deprotection as needed.

Alternatively, the compound of the formula (VIIIa-2a) can be obtained by removing, as needed in an appropriate manner, the protecting group of the nitrogen atom of  $Q^{3d}$  from the compound which is available by the below-described

preparation process and is represented by the following  
formula (VIIIa-2c):



[wherein  $X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$ ,  $X^7$  and  $X^8$  have the same meanings as  
described above and  $Q^{3d}$  means any one of the following  
groups:



(wherein, when the carbon atom to which each of  $R^{30}$ ,  $R^{31}$ ,  $R^{32}$   
and  $R^{33}$  has been bonded is not adjacent to a nitrogen atom,  
 $R^{30}$ ,  $R^{31}$ ,  $R^{32}$  and  $R^{33}$  each independently represents

- a hydrogen atom,
- an alkyl group,
- a hydroxyl group,
- a hydroxyl group protected with a methoxymethyl or  
tetrahydropyranyl or the like group,
- a hydroxyalkyl group,

a hydroxyalkyl group having a hydroxyl group protected with a methoxymethyl or tetrahydropyranyl or the like group,

an alkoxyl group,

5 an alkoxyalkyl group,

a dialkoxyalkyl group,

a dialkylamino group,

a monoalkylamino group having an amino group protected with a tertiary butoxycarbonyl group,

10 a dialkylaminoalkyl group,

a monoalkylaminoalkyl group having an amino group protected with a tertiary butoxycarbonyl group,

a dialkylaminocarbonyl group,

a dialkylaminocarbonylalkyl group,

15 a dialkylaminoalkyloxy group,

a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a monoalkylaminocarbonylalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

20 a dialkylaminocarbonylalkyloxy group,

a dialkylaminoalkyloxy group,

a monoalkylaminoalkyloxy group having an amino group protected with a tertiary butoxycarbonyl group,

a carbamoyl group,

25 a monoalkylcarbamoyl group,

a dialkylcarbamoyl group,

- a carbamoylalkyl group,  
a monoalkylcarbamoylalkyl group,  
a dialkylcarbamoylalkyl group,  
a pyrrolidinocarbonyl group,  
5 a pyrrolidinocarbonylalkyl group,  
a piperidinocarbonyl group,  
a piperidinocarbonylalkyl group,  
a morpholinocarbonyl group,  
a morpholinocarbonylalkyl group,  
10 a dialkylaminocarbonylalkyloxy group, or the like;  
when the carbon atom to which each of  $R^{30}$ ,  $R^{31}$ ,  $R^{32}$  and  $R^{33}$   
has been bonded is adjacent to a nitrogen atom,  $R^{30}$ ,  $R^{31}$ ,  $R^{32}$   
and  $R^{33}$  each independently represents  
a hydrogen atom,  
15 an alkyl group,  
a hydroxyalkyl group having a hydroxy group protected  
with a methoxymethyl, tetrahydropyranyl or the like group,  
an alkoxyalkyl group,  
a dialkoxyalkyl group,  
20 a dialkylaminoalkyl group,  
a monoalkylaminoalkyl group having an amino group pro-  
tected with a tertiary butoxycarbonyl group,  
a dialkylaminocarbonyl group,  
a dialkylaminocarbonylalkyl group,  
25 a carbamoyl group,  
a monoalkylcarbamoyl group,



a carbamoylalkyl group,  
a monoalkylcarbamoylalkyl group,  
a pyrrolidinocarbonyl group,  
a pyrrolidinocarbonylalkyl group,  
5 a piperidinocarbonyl group,  
a piperidinocarbonylalkyl group,  
a morpholinocarbonyl group,  
a morpholinocarbonylalkyl group,  
a dialkylaminoalkyloxyalkyl group or the like;

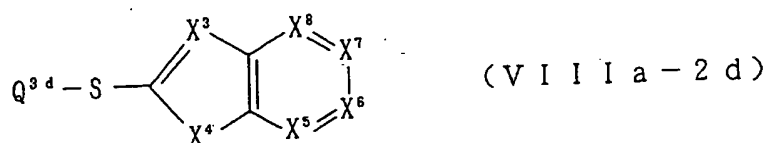
10  $R^{30}$  and  $R^{31}$ , or  $R^{32}$  and  $R^{33}$  may be coupled together to  
form a saturated or unsaturated 5- to 7-membered cyclic hy-  
drocarbon group which may have a substituent or a saturated  
or unsaturated 5- to 7-membered heterocyclic group which  
may have a substituent;

15  $R^{34}$  represents  
an alkyl group,  
a hydroxyalkyl group having a protected hydroxyl  
group,  
a hydroxyalkylcarbonyl group having a protected hy-  
20 droxyl group,  
a hydroxyalkylsulfonyl group having a protected hy-  
droxyl group,  
an alkoxyalkyl group,  
an alkoxyalkylcarbonyl group,  
25 an alkoxyalkylsulfonyl group,  
an alkylcarbonyl group,

an alkylcarbonylalkyl group,  
 an alkylsulfonyl group,  
 an alkylsulfonylalkyl group,  
 an alkoxycarbonyl group,  
 5 an alkoxycarbonylalkyl group,  
 an alkoxycarbonylalkylcarbonyl group,  
 an alkoxycarbonylalkylsulfonyl group,  
 a dialkylaminoalkyl group,  
 a monoalkylaminoalkyl group having an amino group pro-  
 10 tected with a tertiary butoxycarbonyl group,  
 a dialkylaminocarbonyl group,  
 a dialkylaminocarbonylalkyl group or the like;  
 $R^{32}$  and  $R^{34}$ , or  $R^{33}$  and  $R^{34}$  may be coupled together to  
 form a saturated or unsaturated 5- to 7-membered heterocy-  
 15 clic group which may have a substituent;

$R^{35}$  represents an ordinarily employed protecting group  
 for a nitrogen atom such as tertiary butoxycarbonyl group,  
 benzyl group or triphenylmethyl group; j and k independ-  
 ently represents 0 or an integer of 1; and l stands for an  
 20 integer of 1 to 3 with the proviso that the sum of k and l  
 stands for an integer of 1 to 4)].

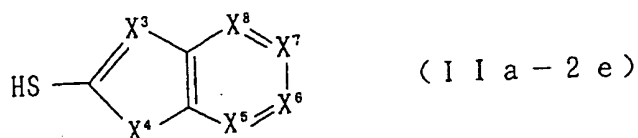
The compound represented by the following formula  
 (VIIIa-2d):



[wherein  $X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$ ,  $X^7$ ,  $X^8$  and  $Q^{3d}$  have the same meanings as described above] can be obtained by reacting an amino compound, which is available in a known manner or by application thereof and is represented by the following formula (IIIc):



[wherein  $Q^{3d}$  has the same meaning as described above] with a fused heterocyclic thiol compound represented by the following formula (IIa-2e):



[wherein  $X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$ ,  $X^7$  and  $X^8$  have the same meanings as described above] in the presence of an appropriate base and oxidizing agent.

The compound of the formula (VIIIa-2c) can be obtained by oxidizing the resulting compound of the formula (VIIIa-2d) in an inert solvent in the presence of an appropriate base.

The compound of the formula (VIIIa-2d) can be obtained by reacting an amino compound, which is represented by the formula (IIIc) and is available in a known manner or by application thereof, with a thiol represented by the formula (IIa-2e) at  $-10$  to  $50^{\circ}\text{C}$  in the presence of an appropriate base and oxidizing agent in water, an alcohol or dioxane or

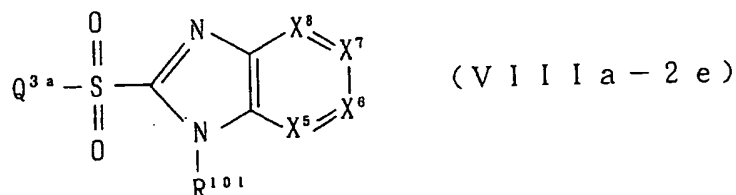
a mixed solvent thereof.

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide. Examples of the oxidizing agent include oxygen, chlorine, bromine, iodine and hypochlorous acid. The compound of the formula (VIIIa-2c) can be obtained by reacting the resulting compound of the formula (VIIIa-2d) with an inorganic oxidizing agent such as potassium permanganate or hydrogen peroxide or an organic oxidizing agent such as 3-chloroperbenzoic acid at  $-30^{\circ}\text{C}$  to  $60^{\circ}\text{C}$  in the presence of an appropriate base in water, alcohol or a mixed solvent thereof.

The protecting group of the nitrogen atom can be removed from the compound of the formula (VIIIa-2c) by an ordinarily employed process. Described specifically, when the nitrogen has been protected with a tertiary butoxycarbonyl group, the protecting group can be removed using an appropriate acid, for example, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid,

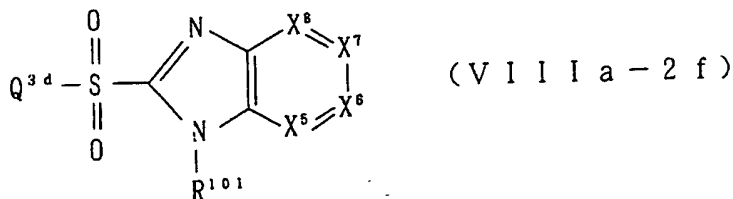
phosphoric acid, trifluoroacetic acid or trifluoromethane-sulfonic acid or combination thereof. The arylmethyl group such as benzyl can also be removed by Birch reduction, in liquid ammonia, in the presence of a metal sodium or by hydrogenolysis in the presence of a palladium-carbon catalyst. By deprotection as described above, the compound represented by the formula (VIIIa-2a) can be obtained.

Among the compounds represented by the formula (VIIIa-2a), the compound of the following formula (VIIIa-2e):



[wherein  $X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$ ,  $X^7$ ,  $X^8$ ,  $R^{101}$  and  $Q^{3a}$  have the same meanings as described above] can also be obtained by removing the protecting group of the nitrogen atom from  $Q^{3d}$  of the compound which is available by the below-described preparation process and is represented by the formula (VIIIa-2f).

Described specifically, the compound of the following formula (VIIIa-2f):

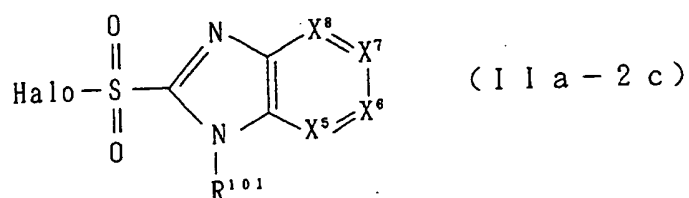


[wherein  $X^5$ ,  $X^6$ ,  $X^7$ ,  $X^8$ ,  $R^{101}$  and  $Q^{3d}$  have the same meanings

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essary in the presence of a Lewis acid such as ferric chloride as a catalyst. As the halogen, a chlorine gas is used. The reaction of the resulting acid chloride (IIa-2c) with the amine of the formula (IIIc) is carried out at -20 to 50°C, if necessary in the presence of a base, in a solvent, for example, water, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform or acetone or a mixed solvent thereof, whereby the compound of the formula (VIIIa-2f) can be obtained.

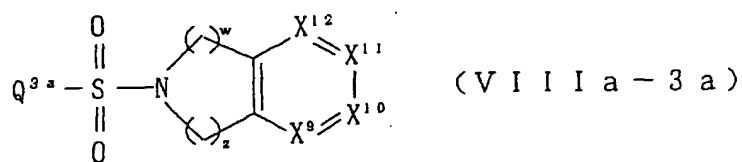
Specific examples of the base include carbonates, alkoxides and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

The protecting group of the nitrogen atom of the compound represented by the formula (VIIIa-2f) can be removed by the ordinarily employed process. Described specifically, when the protecting group is a tertiary butoxycarbonyl group, it can be removed by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or

trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. A triphenylmethyl group can be removed by using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. The arylmethyl group such as benzyl group can also be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIIIa-2e) can be obtained.

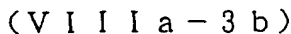
<Synthesis of the compound of the formula (VIIIa-3a)>

Among the compounds of the formula (VIIIa), the compound of the following formula (VIIIa-3a):

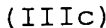


[wherein  $\text{X}^9$ ,  $\text{X}^{10}$ ,  $\text{X}^{11}$ ,  $\text{X}^{12}$ ,  $\text{Q}^{3a}$ ,  $w$  and  $z$  have the same meanings as described above] can be obtained by removing the protecting group from the nitrogen atom of  $\text{Q}^{3d}$  of the compound which is available by the below-described preparation process and is represented by the following formula (VIIIa-3b):

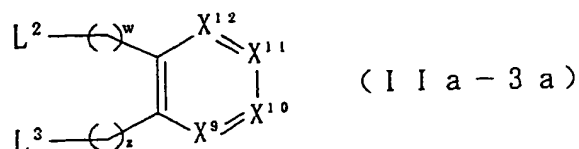




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[wherein,  $Q^{3d}$  has the same meaning as described above] and then reacting the resulting compound of the formula (XV) with a compound represented by the following formula (IIa-3a):



[wherein,  $X^9$ ,  $X^{10}$ ,  $X^{11}$ ,  $X^{12}$ ,  $w$  and  $z$  have the same meanings as described above,  $L^2$  and  $L^3$  each independently represents an eliminating group frequently employed in organic chemistry such as chlorine, bromine, iodine, methylsulfonyloxy or paratoluenesulfonyloxy] in the presence of an appropriate base in an inert solvent.

The reaction between the compounds of the formula (IIIC) and (XIII) is carried out at  $-70$  to  $100^\circ\text{C}$  in an solvent, for example, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, benzene, toluene or acetone, or a mixed solvent thereof in the presence of a base such as sodium carbonate, potassium carbonate, or an organic base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU), whereby the compound of the formula (XIV) can be obtained.

The protecting group on the nitrogen atom of the com-

pound represented by the formula (XIV) can be removed as described below. When the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or combination thereof. An arylmethyl group such as benzyloxycarbonyl, paranitrobenzyloxycarbonyl or paramethoxybenzyloxycarbonyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst. The paramethoxybenzyloxycarbonyl group can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. Thus, by the removal of the protecting group, the compound of the formula (XV) can be obtained.

The reaction of the compound of the formula (XV) with the compound of the formula (IIa-3a) is carried out at -20 to 150°C in the presence of a base in a solvent, for example, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, a solvent such as acetone, or an amide solvent such as N,N-dimethylformamide, N-methylpyrrolidin-2-one or acetamide, or a mixed solvent thereof, whereby the compound of the formula (VIII-3b) can be obtained. Examples of the

base include sodium carbonate, potassium carbonate, sodium hydride, potassium hydride, and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine  
5 and diazabicyclo[5.4.0]undec-7-ene (DBU).

The protecting group of the nitrogen atom of the compound represented by the formula (VIII-3b) can be removed by the ordinarily employed process. Described specifically, when the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid  
10 such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. An arylmethyl group such as benzyl can be removed by the hydrogenolysis in the presence of a palladium-carbon catalyst.  
15 A triphenylmethyl group can be removed using an appropriate acid such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or  
20 combination thereof. The arylmethyl group such as benzyl can also be removed by Birch reduction with a metal sodium in liquid ammonia or by hydrogenolysis in the presence of a palladium-carbon catalyst. Thus, by the removal of the protecting group, the compound of the formula (VIII-3a) can  
25 be obtained.

<Reaction of any one of the compounds of the formulas (IVa)

to (IVd) with the compound of the formula (VIIIa)

Examples of the carboxylic acid of each of the formulas (IVa) to (IVd) in an appropriate activated form include acid mixed acid anhydrides available by reacting the carboxylic acid of each of the formulas (IVa) to (IVd) with a chloroformate ester such as isobutyl chloroformate, thereby converting it into the corresponding acid anhydride, acid halides such as acyl chloride prepared by treating with an inorganic acid halide such thionyl chloride, active esters obtained by reacting with a phenol such as paranitrophenol or pentafluorophenyl-trifluoroacetate, active esters obtained by reacting it with N-hydroxybenztriazole or N-hydroxysuccinimide, reaction products with N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride which is ordinarily employed in the synthesis of an amino acid, reaction products with diethyl cyanophosphonate (Shioiri's method) and reaction products with triphenylphosphine and 2,2'-dipyridylsulfide (Mukaiyama's method).

The resulting carboxylic acid in an activated form is reacted with the compound of the formula (VIIIa) at -78 to 150°C, usually in the presence of an appropriate base in an inert solvent, whereby the sulfonyl derivative of the formula (I) can be obtained.

Examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline

earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium such as lithium diisopropylamide; organometallic base of bissilylamine compounds such as lithium bis(trimethylsilyl)amide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane.

[Preparation Process-2-(1)]

When the nitrogen atom of  $Q^{3a}$  of the compound represented by the below-described formula (VIIIa) to be acylated:



[wherein,  $Q^{3a}$  and  $Q^A$  have the same meanings as described above] is a primary or secondary amine, preferred examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide.

ide; and organic bases such as pyridine, 2,6-lutidine, col-  
 lidine, 4-dimethylaminopyridine, triethylamine, N-  
 methylmorpholine, diisopropylethylamine and diazabicy-  
 clo[5.4.0]undec-7-ene (DBU) and usable examples of the sol-  
 5 vent include, in addition to inert solvents, alcohol sol-  
 vents such as ethanol and butanol and ester solvents such  
 as ethyl acetate.

[Preparation Process-2-(2)]

When the nitrogen atom of  $Q^{3a}$  of the compound repre-  
 10 sented by the below-described formula (VIIIa) to be acy-  
 lated:



[wherein  $Q^{3a}$  and  $Q^A$  have the same meanings as described  
 above] forms an amide bond, examples of the base include  
 15 alkoxides and hydrides of an alkali metal or alkaline earth  
 metal such as sodium ethoxide, potassium butoxide, sodium  
 hydride and potassium hydride; organometallic base com-  
 pounds typified by alkyl lithium such as n-butyl lithium  
 and dialkylaminolithium such as lithium diisopropylamide;  
 20 organometallic base of bissilylamine compounds such as  
 lithium bis(trimethylsilyl)amide; and organic bases such as  
 diazabicyclo[5.4.0]undec-7-ene (DBU). Examples of the in-  
 ert solvent include tetrahydrofuran, 1,2-dimethoxyethane,  
 dioxane and N,N-dimethylformamide.

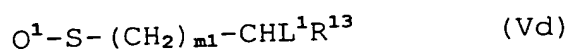
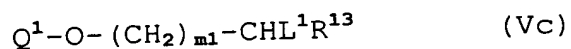
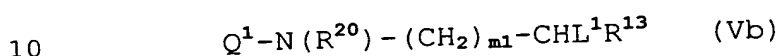
25 [Preparation Process-3]

A process for preparing, in the case the nitrogen atom of

$Q^{3a}$  of the compound represented by the following formula  
(VIIIa):



[wherein,  $Q^{3a}$  and  $Q^A$  have the same meanings as described  
5 above] constitutes an amide, the sulfonyl derivative of the  
present invention by alkylating the nitrogen atom of the  
formula (VIIIa) with any one of the compounds represented  
by the following formulas (Va) to (Vd):



[wherein  $Q^1$ ,  $Q^{2b}$ ,  $R^{13}$ ,  $R^{20}$ ,  $m1$  and  $L^1$  have the same meanings  
as described above].

15 When the nitrogen atom of  $Q^{3a}$  of the compound of the  
formula (VIIIa) is a nitrogen atom of an amide bond, the  
sulfonyl derivative of the formula (I) can be synthesized  
by alkylating the nitrogen atom of  $Q^{3a}$  of the compound of  
the formula (VIIIa) with any one of the compounds of the  
20 formulas (Va) to (Vd). Described specifically, the sul-  
fonyl derivative (I) can be obtained by reacting the com-  
pound of the formula (VIIIa) with any one of the compounds  
of the formulas (Va) to (Vd) at  $-78$  to  $150^\circ\text{C}$  for 0.5 to 120  
hours in the presence of an appropriate base in an inert  
25 solvent, thereby effecting alkylation of the nitrogen atom.



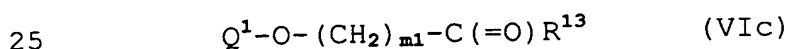
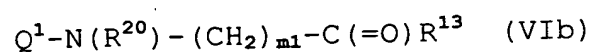
Examples of the base include alkoxides and hydrides of an alkali metal or alkaline earth metal, such as sodium ethoxide, potassium butoxide, sodium hydride and potassium hydride; organometallic base compounds typified by alkyl lithium such as n-butyl lithium and dialkylaminolithium  
 5 such as lithium diisopropylamide; organometallic base of bissilylamine compounds such as lithium bis(trimethylsilyl)amide; and organic bases such as di-azabicyclo[5.4.0]undec-7-ene (DBU). Preferred examples of  
 10 the inert solvent include tetrahydrofuran, 1,2-dimethoxyethane, toluene, dioxane and N,N-dimethylformamide.

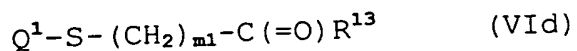
[Preparation Process-4]

A process for preparing, in the case where the nitrogen  
 15 atom of  $Q^{3a}$  of the compound represented by the formula (VIIIa):



[wherein,  $Q^{3a}$  and  $Q^A$  have the same meanings as described above] exists as a primary or secondary amine, the sulfonyl  
 20 derivative (I) by forming the corresponding imine with any one of the carbonyl compounds represented by the following formulas (VIa) to (VIId):





[wherein  $Q^1$ ,  $Q^{2b}$ ,  $R^{13}$ ,  $R^{20}$  and  $m1$  have the same meanings as described above], followed by reduction.

Described specifically, when the nitrogen atom of  $Q^{3a}$  of the compound of the formula (VIIIa) exists as an amine, the sulfonyl derivative of the formula (I) can be prepared by reacting the compound of the formula (VIIIa) with any one of the carbonyl compounds of the formulas (VIa) to (VID) at  $-20$  to  $150^\circ\text{C}$  for 0.5 to 120 hours, usually in an inert solvent, if necessary in the presence of an organic acid such as acetic acid, a mineral acid such as hydrochloric acid or a Lewis acid such as aluminum chloride, thereby forming the corresponding imine and then hydrogenating the resulting imine with a boron hydride reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium tri-  
 15 acetoxymethylborohydride or a catalytic reduction catalyst such as palladium-carbon in an inert solvent at  $10$  to  $110^\circ\text{C}$  for 0.5 to 120 hours.

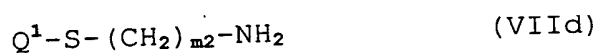
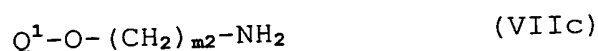
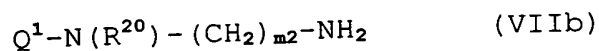
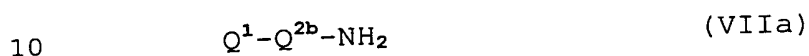
Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane.

## [Preparation Process-5]

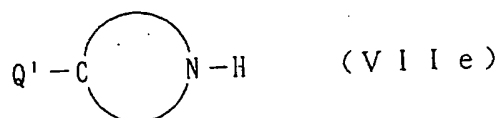
A process for reacting, in the case where  $Q^{3a}$  of the compound represented by the following formula (VIIIa):



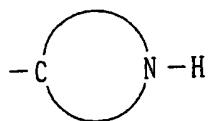
5 [wherein,  $Q^{3a}$  and  $Q^A$  have the same meanings as described above] exists as a primary or secondary amine, the compound of the formula (VIIIa) with any one of the primary-amine-containing compounds represented by the following formulas (VIIa) to (VIId):



or a secondary-amine-containing compound represented by the  
15 following formula (VIIe):



[in the above-described formulas,  $Q^1$ ,  $Q^{2b}$ ,  $R^{20}$ ,  $m2$  and the group:



20 have the same meanings as described above] by using a reagent such as phosgene, triphosgene or carbonyldiimidazole, thereby forming the corresponding urea derivative.

When  $Q^{3a}$  of the compound of the formula (VIIIa) exists as an amine, the compound of the formula (VIIIa) is reacted with any one of the primary-amine-containing compounds represented by the formulas (VIIa) to (VIId) or the secondary-amine-containing compound represented by the formula (VIIe) and the reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole to introduce it into the sulfonyl derivative of the present invention represented by the formula (I), which is to be an urea derivative.

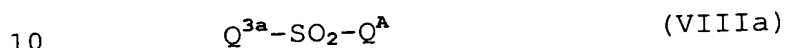
The synthesis can be carried out by successively reacting, with the reagent such as phosgene, triphosgene or 1,1'-carbonyldiimidazole, any one of the primary-amine-containing compounds of the formulas (VIIa) to (VIId) or the secondary-amine-containing compound of the formula (VIIe) and the compound of the formula (VIIIa), if necessary in the presence of a base, in an inert solvent. Examples of the inert solvent include dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulfoxide and sulfolane. Among them, dichloromethane, tetrahydrofuran and toluene are preferred.

Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-

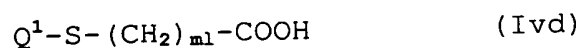
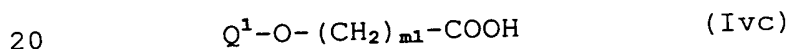
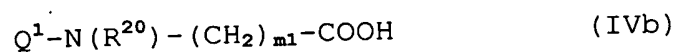
lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction may be conducted at a temperature range of from  $-70^{\circ}\text{C}$  to  $110^{\circ}\text{C}$ .

5 [Preparation Process-6]

A process for preparing a urea-containing sulfonyl derivative of the formula (I) by reacting, in the case where the nitrogen atom of  $\text{Q}^{3a}$  of the compound represented by the formula (VIIIa):



[wherein,  $\text{Q}^{3a}$  and  $\text{Q}^A$  have the same meanings as described above] exists as a primary or secondary amine, the amine of the formula (VIIIa) with a known isocyanate derivative ( $\text{Q}^1-\text{Q}^{2b}-\text{N}=\text{C}=\text{O}$ ) [wherein,  $\text{Q}^1$  and  $\text{Q}^{2b}$  have the same meanings as described above] or an isocyanate prepared from any one of the carboxylic acids represented by the following formulas (IVa) to (IVd):



[wherein  $\text{Q}^1$ ,  $\text{Q}^{2b}$ ,  $\text{R}^{20}$  and  $m1$  have the same meanings as described above].

When  $\text{Q}^{3a}$  of the compound represented by the formula (VIIIa) is an amine, the sulfonyl derivative of the formula

25

(I) can be prepared by reacting the compound of the formula (VIIIa) with a known isocyanate derivative at -20 to 100°C for 0.5 to 120 hours in an inert solvent.

The isocyanate derivative can be synthesized from any one of the carboxylic acids of the formulas (IVa) to (IVd). Described specifically, it can be obtained by introducing any one of the carboxylic acids of the formulas (IVa) to (IVd) into the corresponding acid halide with thionyl chloride, oxalyl chloride or the like, reacting the resulting acid halide with sodium azide at a temperature range of from 0 to 60°C in an inert solvent and then, heating the reaction mixture; by reacting the carboxylic acid of the formula (IVa) with a chloroformate such as isobutyl chloroformate, reacting the resulting acid anhydride with sodium azide and then heating the reaction mixture; or introducing any one of the carboxylic acids represented by the formulas (IVa) to (IVd) into the corresponding hydrazide through an ester in an inert solvent such as tetrahydrofuran, chloroform or toluene at -20 to 110°C, reacting the resulting hydrazide with nitrous acid or alkyl ester thereof to introduce it into the corresponding acylazide and then heating at 20 to 150°C in a solvent such as chloroform, dichloroethane, toluene, xylene or N,N-dimethylformamide.

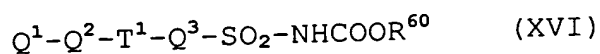
The sulfonyl derivative of the formula (I) can also be prepared by reacting any one of the carboxylic acids of the formulas (IVa) to (IVd) with diphenylphosphorylazide at 10

to 100°C in the presence of a base such as triethylamine in an inert solvent.

[Preparation Process-7]

The compound represented by the following formula

(XVI):



[wherein,  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $R^{60}$  and  $T^1$  have the same meanings as described above] can be synthesized by reacting, in the case where the nitrogen atom of  $Q^{3a}$  of the compound represented by the following formula (Ia) to be sulfonylated:

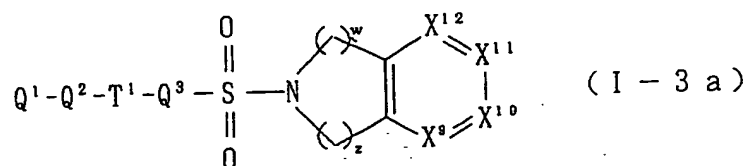


[wherein,  $Q^1$ ,  $Q^2$ ,  $Q^{3a}$  and  $T^1$  have the same meanings as described above] exists as a primary or secondary amine, the compound of the formula (Ia) with a compound which is available from chlorosulfonyl isocyanate and an alcohol and is represented by the following formula (XIII):



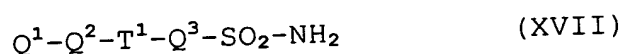
[wherein,  $R^{60}$  has the same meaning as described above] in the presence of an appropriate base in an inert solvent.

The compound represented by the following formula (I-3a):

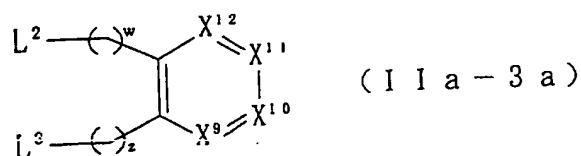


[wherein,  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $T^1$ ,  $X^9$ ,  $X^{10}$ ,  $X^{11}$ ,  $X^{12}$ ,  $w$  and  $z$  have the

same meanings as described above], one of the compounds of the formula (I), can be synthesized by removing the protecting group on the nitrogen atom of the resulting compound (XVI), thereby obtaining a compound represented by the following formula (XVII):



[wherein,  $Q^1$ ,  $Q^2$ ,  $Q^3$  and  $T^1$  have the same meanings as described above]; and then reacting the resulting compound of the formula (XVII) with a compound represented by the following formula (IIa-3a):



[wherein,  $X^9$ ,  $X^{10}$ ,  $X^{11}$ ,  $X^{12}$ ,  $L^2$ ,  $L^3$ ,  $w$  and  $z$  have the same meanings as described above] in an appropriate base in an inert solvent.

The reaction between the compound of the formula (Ia) and the compound of the formula (XIII) to synthesize the compound of the formula (XVI) is effected at  $-70$  to  $100^\circ C$  in an solvent, for example, an ether solvent such as diethyl ether, tetrahydrofuran, dimethoxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, or a solvent such as benzene, toluene or acetone or a mixed solvent thereof and in this reaction, usable examples of the base include sodium carbonate, potassium carbonate and or-



ganic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

5       The protecting group on the nitrogen atom of the compound of the formula (XVI) can be removed as described below. When the protecting group is a tertiary butoxycarbonyl group, it can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, 10       sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or combination thereof. An arylmethyl group such as benzyloxycarbonyl, paranitrobenzyloxycarbonyl or paramethoxybenzyloxycarbonyl can be removed by the hydrogenolysis in the presence of a palladium-carbon 15       catalyst. The paramethoxybenzyloxycarbonyl group can be removed using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof. Thus, by the removal of the 20       protecting group, the compound of the formula (XVII) can be obtained.

      The reaction of the compound of the formula (XVII) with the compound of the formula (IIa-3a) is carried out at -20 to 150°C in the presence of a base in a solvent, for 25       example, an alcohol solvent such as ethanol, an ether solvent such as diethyl ether, tetrahydrofuran, dimeth-

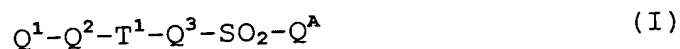
oxyethane or dioxane, a halogen solvent such as dichloromethane or chloroform, a solvent such as acetone, N,N-dimethylformamide, N-methylpyrrolidin-2-one or acetamide, or a mixed solvent thereof, whereby the compound of the formula (I-3a), one of the compounds of the formula (I), can be obtained.

Examples of the base include sodium carbonate, potassium carbonate, and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

From the compound of the formula (I-3a), it is possible to eliminate the protecting group in an ordinarily employed process if necessary.

#### [Preparation Process-8]

A process for synthesizing a sulfonyl derivative represented by the following formula (I):



[wherein,  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$ ,  $T^1$  have the same meanings as described above] by coupling reaction using a transition metal catalyst.

When in the structure of  $Q^1$  of the sulfonyl derivative of the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, it can be subjected to coupling reaction with a bo-

ric-acid-substituted aryl compound in the presence of a transition metal catalyst.

When in the structure of  $Q^1$  of the sulfonyl derivative of the formula (I), an alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group in the presence of a transition metal catalyst.

When in the structure of  $Q^1$  of the sulfonyl derivative represented by the formula (I), a boric-acid-substituted aryl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl compound or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl compound.

When in the structure of  $Q^1$  of the sulfonyl derivative of the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group or a halogen- or trifluoromethanesulfonyloxy-substituted alkenyl group is contained, it can be subjected to coupling reaction with a boric-acid-substituted aryl derivative by using a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (O), in a two-phase solvent such as benzene-water or toluene-water, an amide solvent such as N,N-dimethylformamide or an ether solvent such as tetrahydrofuran or dimethoxyethane, in the presence of a base such as sodium carbonate, sodium hydroxide, barium hydroxide, potassium phosphate or cesium carbonate or a

neutral salt such as cesium fluoride at a temperature range of 20 to 150°C for 0.5 to 120 hours.

When in the structure of  $Q^1$  of the sulfonyl derivative represented by the formula (I), an alkenyl group or boric-  
5 acid-substituted alkenyl group is contained, it can be subjected to coupling reaction with a halogen- or trifluoromethanesulfonyloxy-substituted aryl group by using a transition metal catalyst such as palladium acetate, in the presence of an appropriate base, in an amide solvent such  
10 as N,N-dimethylformamide at a temperature range of from 20 to 150°C for 0.5 to 120 hours.

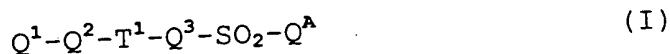
When in the structure of  $Q^1$  of the sulfonyl derivative represented by the formula (I), a halogen- or trifluoromethanesulfonyloxy-substituted aryl group, it can be sub-  
15 jected to coupling reaction with an alkenyl compound by using a transition metal catalyst. By the above-described process, the sulfonyl derivative of the formula (I) can be obtained. From the sulfonyl derivative of the formula (I) can be obtained. By deprotection, the sulfonyl derivative  
20 of the formula (I) having a changed substituent can be obtained.

#### [Preparation Process-9]

A process for preparing each of a thioamido type sulfonamide product, an amidoxime type sulfonamide product and a  
25 hydrazono type sulfonamide product:

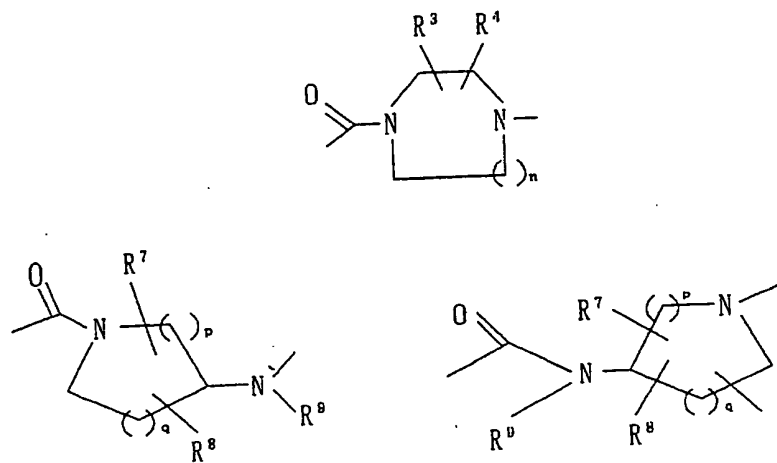
When  $T^1-Q^3$  of the sulfonyl derivative represented by

the following formula (I):



[wherein  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  and  $T^1$  have the same meanings as described above] represents any one of the following formu-

5 las:



[wherein  $R^3$ ,  $R^4$ ,  $R^7$ ,  $R^8$  and  $R^9$  have the same meanings as described above,  $n$  stands for an integer of 1 or 2,  $p$  stands for an integer of 1 to 3 and  $q$  stands for an integer of 0 to 3 with the proviso that the sum of  $p$  and  $q$  stands for an integer of 3 or 4] and none of amine-, alkylamine-, amido-, hydroxyl- and carboxylic-acid-containing substituents exist on  $R^3$ ,  $R^4$ ,  $R^7$ ,  $R^8$ ,  $R^9$  or a substituent substitutable there-  
 10 for in  $Q^1$ ,  $Q^2$  and  $Q^3$  of the formula (I),  
 15 a thioamido type sulfonamide derivative (I) can be obtained by reacting the sulfonyl derivative represented by the formula (I) with a diphosphorous pentasulfide or Lawson reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) at  $-30$  to  $150^\circ\text{C}$ , if necessary in an inert solvent

at 0 to 120°C. Examples of the inert solvent include alkyl halide solvents such as dichloromethane, chloroform and carbon tetrachloride, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane and aromatic solvents such as benzene and toluene, and a mixture thereof.

The sulfonamide derivative represented by the formula (I) can be obtained by reacting the obtained thioamido type sulfomide with a hydroxylamine, alkoxyamine which may have a substituent, and hydrazine which may have a substituent, or a salt thereof, in the presence of a mercury catalyst such as a mercury (II) chloride at -30 to 150°C if necessary, or in an appropriate solvent 0 to 120°C if necessary.

Examples of the solvent include alcohol solvents such as ethanol, alkyl halide solvents such as dichloromethane, chloroform and carbon tetrachloride, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane and aromatic solvents such as benzene and toluene, and a mixture thereof.

The sulfonyl derivative represented by the formula (I) can be obtained by reacting the sulfonyl derivative of the formula (I) with a halogenating agent such as phosphorous oxychloride or phosphorus pentachloride or an alkylating agent such as Meerwein reagent at -30 to 140°C, if necessary in an inert solvent, for example, a halogen solvent such as chloroform at 0 to 80°C, to convert the derivative into the corresponding imino chloride or imino ether and

then, reacting the resulting imino chloride or imino ether with hydroxylamine, alkoxyamine which may have a substituent or salt thereof at 0 to 80°C, preferably at 20 to 60°C, if necessary in the presence of a base catalyst.

5        Examples of the inert solvent include alkyl halide solvents such as dichloromethane, chloroform and carbon tetrachloride, ether solvents such as tetrahydrofuran, 1,2-dimethoxyethane and dioxane and aromatic solvents such as benzene and toluene. Among them, the alkyl halide solvents  
10       are particularly preferred. Examples of the base include carbonates, alkoxides, hydroxides and hydrides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride and  
15       potassium hydride; organometallic base compounds typified by an alkyl lithium such as n-butyl lithium and a dialkylamino lithium such as lithium diisopropylamide; organometallic base of bis(silyl)amine compounds such as lithium bis(trimethylsilyl)amide; and organic bases such as pyri-  
20       dine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[Preparation Process-10]

N-oxide formation

25       When in the sulfonyl derivative of the formula (I), there exists a nitrogen-containing heterocyclic aromatic

ring or aliphatic tertiary amine on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, the sulfonyl derivative of the formula (I) is reacted with a peroxide such as hydrogen peroxide, metachloroperbenzoic acid or tertiary butyl hydroperoxide at  $-40$  to  $60^\circ\text{C}$  for 0.5 to 120 hours preferably  $-20$  to  $20^\circ\text{C}$  in a solvent such as water, acetic acid, a benzene solvent such as benzene, toluene or xylene, an ether solvent such as tetrahydrofuran or dimethoxyethane or an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, whereby the sulfonyl derivative of the formula (I) can be obtained as an N-oxide derivative.

[Preparation Process-11]

Quaternization of a nitrogen atom

When in the sulfonyl derivative of the formula (I), there exists a nitrogen-containing heterocyclic aromatic group or aliphatic tertiary amine on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, the sulfonyl derivative of the formula (I) is reacted with an alkyl halide such as methyl iodide or ethyl iodide in an ether solvent such as 1,2-dimethoxyethane or dioxane, an aromatic solvent such as benzene or toluene, an amide solvent such as N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidin-2-one or a sulfoxide solvent such as dimethyl sulfoxide or sulfolane at  $-10$  to  $150^\circ\text{C}$ , preferably 0 to  $80^\circ\text{C}$ , whereby the sulfonyl derivative of the formula (I)



can be obtained as a quaternary amino product.

[Preparation Process-12]

Sulfoxide or sulfone formation

5 When in the sulfonyl derivative of the formula (I), a sulfur-containing hetero ring or aliphatic thioether exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, the sulfonyl derivative of the formula (I) is reacted with a peroxide such as hydrogen peroxide, metachloroperbenzoic acid or tertiary butyl hydroperoxide at -40 to 10 60°C for 0.5 to 120 hours, preferably -20 to 20°C in a solvent such as water or acetic acid, a benzene solvent such as benzene, toluene or xylene, an ether solvent such as tetrahydrofuran or dimethoxyethane or an alkyl halide solvent such as dichloromethane, chloroform or carbon tetra- 15 chloride, whereby the sulfonyl derivative (I) can be obtained in the form of sulfoxide or sulfone.

[Preparation Process-13]

Amidino formation-1

20 When in the sulfonyl derivative of the formula (I), a nitrile group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, it can be converted into an amidino group by an ordinarily employed process. The amidino-containing sulfonyl derivative of the formula (I) can be obtained, for example, by allowing an equal amount to 25 large excess of a  $C_{1-4}$  alcohol such as methanol, ethanol or propanol to act on the sulfonyl derivative of the formula

(I) at -10 to 60°C for 3 to 120 hours in an aliphatic ether solvent such as diethyl ether, an alkyl halide solvent such as chloroform or dichloromethane or an aprotic solvent such as benzene or a mixed solvent thereof in the presence of a hydrogen halide such as hydrogen chloride or hydrogen bromide, thereby converting it to the corresponding imino ether; then reacting the resulting imino ether product with ammonium, a monoalkylamine which may have a substituent or a dialkylamine which may have a substituent, or a carbonate or acetate thereof at -10 to 140°C for 0.5 to 200 hours in a C<sub>1-4</sub> alcohol such as ethanol or propanol, an aliphatic ether solvent such as diethyl ether, an alkyl halide solvent such as chloroform, an aprotic solvent such as benzene, a solvent such as N,N-dimethylformamide or dimethylsulfoxide or a mixed solvent thereof, preferably at -8 to 30°C for 10 to 96 hours in ethanol.

[Preparation Process-14]

#### Amidino formation-2

When in the sulfonyl derivative of the formula (I), a primary or secondary amino group exists on Q<sup>1</sup>, Q<sup>2</sup>, Q<sup>3</sup>, Q<sup>A</sup> or T<sup>1</sup> or a substituent substitutable therefor, it can be converted into a substituted amidino group by an ordinarily employed process.

Described specifically, the amidino-containing sulfonyl derivative of the formula (I) can be obtained, for example, by reacting the sulfonyl derivative of the formula

(I) with an imino ether, imino chloride or salt thereof, which has been synthesized from an amide compound or nitrile compound, in an aliphatic ether solvent such as diethyl ether, an alkyl halide solvent such as chloroform or dichloromethane or an aprotic solvent such as benzene, or a mixed solvent thereof, if necessary in the presence of a base catalyst, at -10 to 140°C for 0.5 to 200 hours, preferably 0 to 80°C for 10 to 96 hours. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

#### [Preparation Process-15]

##### N-nitrile formation

When in the sulfonyl derivative of the formula (I), a primary or secondary amine group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, it can be cyanated by an ordinarily employed process.

For example, the sulfonyl derivative of the formula (I) is reacted with cyan bromide in an alcohol solvent such as methanol, ethanol or propanol in the presence of a salt such as sodium acetate or a base at -10 to 110°C, preferably 0 to 60°C, whereby the sulfonyl derivative (I) having a

nitrile group on its nitrogen atom can be obtained. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[Preparation Process-16]

#### 10 Amidoxime or carboxamido-O-alkyloxime introduction

When in the sulfonyl derivative of the formula (I), a nitrile group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, it can be converted into an amidoxime or carboxamido-O-alkyloxime group by an ordinarily employed process.

For example, the sulfonyl derivative of the formula (I) is reacted with hydroxylamine or an alkoxyamine which may have a substituent, or salt thereof in an alcohol solvent such as methanol, ethanol or propanol, an ether solvent such as diethyl ether or tetrahydrofuran, a halogenated hydrocarbon such as chloroform or dichloromethane, an aprotic solvent such as toluene, an amide solvent such as N,N-dimethylformamide or a solvent such as dimethylsulfoxide, or a mixed solvent thereof at  $-10$  to  $110^\circ\text{C}$ , preferably  $0$  to  $60^\circ\text{C}$ , if necessary in the presence of a base catalyst, whereby the sulfonyl derivative of the formula (I) having

an amidoxime or carboxamido-O-alkyloxime group can be obtained. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[Preparation Process-17]

#### 10 Guanidino introduction

When in the sulfonyl derivative of the formula (I), a primary or secondary amino group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, it can be converted into a substituted or unsubstituted guanidino group by an ordinarily employed process.

For example, the sulfonyl derivative of the formula (I) having a primary or secondary amino group is reacted with N,N'-di(tert-butoxy)carbonylthiourea and N,N'-dicyclohexylcarbodiimide as a condensing agent in an aliphatic ether solvent such as diethyl ether, a halogenated hydrocarbon such as chloroform or dichloromethane or an aprotic solvent such as benzene, or a mixed solvent thereof at -10 to 140°C for 0.5 to 200 hours, preferably 0 to 80°C for 10 to 96 hours, if necessary in the presence of a base catalyst, and then, as usual, the tertiary butoxycarbonyl group is removed, whereby the sulfonyl derivative of the

formula (I) as a guanidino compound can be synthesized. Examples of the base include carbonates and hydroxides of an alkali metal or alkaline earth metal, such as sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; and organic bases such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, N-methylmorpholine, diisopropylethylamine and diazabicyclo[5.4.0]undec-7-ene (DBU).

[Preparation Process-18]

10 Deprotection from the protected nitrogen atom

When in the sulfonyl derivative of the formula (I), an acylamino or alkoxycarbonylamino group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, an amino-containing derivative can be obtained by subjecting the derivative to hydrolysis at 0 to 80°C in a solvent such as water, a lower alcohol or tetrahydrofuran, or a mixed solvent thereof in the presence of a base such as an alkali metal hydroxide e.g. lithium hydroxide, sodium hydroxide or potassium hydroxide. The nitrogen atom to which an acyl type protecting group such as tertiary butoxycarbonyl or paramethoxybenzyloxycarbonyl has been bonded can be converted into a nitrogen-hydrogen bond by using an appropriate acid such as acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid or combination thereof in a solvent such as water, an alcohol solvent such

as methanol, an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, an ether solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane or an aromatic solvent such as benzene or toluene and removing the acyl type protecting group from the nitrogen atom at 0 to 80°C.

The nitrogen atom to which an arylmethoxycarbonyl group such as benzyloxycarbonyl, paramethoxybenzyloxycarbonyl or para(ortho)-nitrobenzyloxycarbonyl has been bonded can be converted into a nitrogen-hydrogen bond by removing the arylmethoxycarbonyl group from the protected nitrogen atom through hydrogenolysis in the presence of a palladium-carbon catalyst in a solvent such as water, an alcohol solvent such as ethanol, an ester solvent such as ethyl acetate, an ether solvent such as diethyl ether or tetrahydrofuran, or a solvent such as acetic acid or N,N-dimethylformamide, or a mixed solvent thereof. The nitrogen atom to which a silyl type protecting group such as trimethylsilyl or tertiary butyl dimethylsilyl has been bonded can be converted into a nitrogen-hydrogen bond by reacting with hydrochloric acid or a hydrofluoride such as tetrabutylammonium fluoride at 0 to 80°C in an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, an ether solvent such as tetrahydrofuran, 1,2-dimethoxyethane or dioxane or an aromatic solvent such as benzene or toluene, thereby removing the silyl group from

the protected nitrogen atom. The nitrogen atom to which a benzyl group has been bonded can be converted into a nitrogen-hydrogen bond by removing the benzyl group through the catalytic reduction at 0 to 80°C with a palladium-carbon catalyst or the like in a solvent such as ethanol, tetrahydrofuran or acetic acid or through the Birch's reduction with a metal sodium in a liquid ammonia. The nitrogen atom to which a triphenylmethyl group has been bonded can be converted into a nitrogen-hydrogen bond by removing the triphenylmethyl group through the catalytic reduction with a palladium-carbon catalyst or the like at 0 to 80°C in a solvent such as ethanol, tetrahydrofuran or acetic acid or through the Birch's reduction with a metal sodium in a liquid ammonia. The removal of the triphenylmethyl group and conversion into a nitrogen-hydrogen bond can also be carried out by using an appropriate acid, such as formic acid, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, trifluoroacetic acid or trifluoromethanesulfonic acid, or a combination thereof at 0 to 80°C.

[Preparation Process-19]

#### Ester hydrolysis

When in the sulfonyl derivative of the formula (I), an alkoxy carbonyl group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, in the case of a methyl or ethyl ester, the alkoxy carbonyl group can be converted



into the corresponding carboxylic acid by the hydrolysis with an appropriate base, for example, an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide. In the case of a tertiary butyl ester, the tertiary butyl group can be removed by treating with trifluoroacetic acid or hydrochloric acid, while in the case of an arylmethyl type ester such as benzyl, the carboxylic acid can be obtained by removing the arylmethyl group by hydrogenolysis in the presence of a palladium-carbon catalyst. Conversion from an ester group to a carboxylic acid residue can be effected using potassium trimethylsilanolate.

[Preparation Process-20]

When in the sulfonyl derivative of the formula (I), an acyloxy, arylmethoxy, silylether, methoxymethyl or tetrahydropyranyl group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, the acyl group such as alkanoyl or aroyl can be removed by the hydrolysis with an appropriate base, for example, an alkali metal hydroxide such as lithium hydroxide, sodium hydroxide or potassium hydroxide; or alternatively can be removed by reacting with an organic base such as ammonia or methylamine. The arylmethyl type protecting group can be removed by the hydrogenolysis with a palladium-carbon catalyst. The silylether group such as tertiary butyl dimethylsilyl can be removed by a hydrofluoride salt such as tetrabutylammonium fluo-

ride. The methoxymethyl or tetrahydropyranyl group can be removed using acetic acid or hydrochloric acid.

[Preparation Process-21]

5 When in the sulfonyl derivative of the formula (I), an amino group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, it can be acylated by an ordinarily employed process which uses an acyl halide or activated carboxylic acid. Alternatively, it can be alkylated by re-

10 ductive alkylation or the like process. The sulfonyl derivative of the formula (I) which is an urea derivative can be prepared by sulfonylation through sulfonic acid chloride or by reacting with isocyanate or carboxylic-acid-derived isocyanate.

[Preparation Process-22]

15 When in the sulfonyl derivative of the formula (I), an carboxyl group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, it can be converted into a carbamoyl, alkylcarbamoyl or dialkylcarbamoyl group by an ordinarily employed active ester method or mixed acid anhydride method and then converted into a hydroxyl or aldehyde

20 group by reduction. The resulting hydroxyl or aldehyde group can be subjected to conversion of a functional group, such as ether bond formation, conversion into an amino group or conversion into an alkylamino group by the process

25 ordinarily employed in organic chemistry. The carboxyl group, after conversion into its ester or mixed acid anhy-

drude directly or by the usual process, is reduced, whereby the corresponding alcohol can be obtained.

[Preparation-23]

Formation of phenol

5        When in the sulfonyl derivative of the formula (I), an aryl-substituted methoxy group exists on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^A$  or  $T^1$  or a substituent substitutable therefor, it can be converted into a hydroxyl group by removing the methyl group using trimethylsilyl iodide at  $-78$  to  $110^\circ\text{C}$  in an alkyl  
10        halide solvent such as dichloromethane, chloroform or carbon tetrachloride or a benzene solvent such as toluene, or at  $-78$  to  $110^\circ\text{C}$  in a Lewis acid such as aluminum chloride, phosphorus tribromide or boron trifluoride, an alkyl halide solvent or an ether solvent.

15        [Preparation process-24]

Conversion of a halogen atom into an alkynyl group

20        When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) has an aromatic  
25        ring substituted with chlorine, bromine or iodine, such a halogen atom can be converted into an acetylene group by

reacting with a silylacetylene compound in the presence of a transition metal catalyst.

The conversion of chlorine, bromine or iodine into a silylacetylene group can be carried out by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) having an aromatic ring substituted with chlorine, bromine or iodine, with a silylacetylene such as trimethylsilylacetylene by using palladium acetate and triphenylphosphine at a temperature range of from -20 to 150°C for 0.5 to 120 hours, if necessary in the presence of a base such as triethylamine or pyridine, in a benzene solvent such as toluene, an ether solvent such as tetrahydrofuran or an amide solvent such as N,N-dimethylformamide, or a mixed solvent thereof.

The silyl group can be removed from the resulting silylacetylene compound by treating the compound with a base such as potassium carbonate, potassium bicarbonate or sodium hydroxide in a solvent, for example, an alcohol solvent such as methanol, an ether solvent such as tetrahydrofuran, water, or a mixed solvent thereof.

## [Preparation Example-25]

## Conversion of a halogen atom into a nitrile group

When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) has an aromatic ring substituted with chlorine, bromine or iodine, such a halogen atom can be converted into a nitrile group by reacting with zinc cyanide in the presence of a transition metal catalyst. The conversion of chlorine, bromine or iodine into a nitrile group can be carried out by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) having an aromatic ring substituted with chlorine, bromine or iodine, with zinc cyanide by using a transition metal catalyst such as tetrakis(triphenylphosphine)palladium (0) at a temperature

range of from -20 to 150°C for 0.5 to 120 hours, if necessary in the presence of a base such as triethylamine or pyridine, in a benzene solvent such as toluene, an ether solvent such as tetrahydrofuran or an amide solvent such as N,N-dimethylformamide, or a mixed solvent thereof.

[Preparation process-26]

Conversion of a halogen atom into a trifluoromethyl group

When the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the formula (VIIIa-2c), the compound of the formula (VIIIa-2d), the compound of the formula (VIIIa-2e), the compound of the formula (VIIIa-3a), or the compound of the formula (VIIIa-3b) contains chlorine, bromine or iodine as a substituent, such a halogen atom can be converted into a trifluoromethyl group by reacting the compound with a trifluoromethylating reagent in the presence of a metal catalyst. Described specifically, the conversion of chlorine, bromine or iodine into a trifluoromethyl group can be effected by reacting the compound of the formula (I), the compound of the formula (VIIIa), the compound of the formula (VIIIa-1b), the compound of the formula (VIIIa-1c), the compound of the formula (VIIIa-2a), the compound of the formula (VIIIa-2b), the compound of the

formula (VIIIa-2c), the compound of the formula (VIIIa-2d),  
the compound of the formula (VIIIa-2e), the compound of the  
formula (VIIIa-3a), or the compound of the formula (VIIIa-  
3b) containing chlorine, bromine or iodine as a substitu-  
ent, with a trifluoromethylating reagent such as methyl  
2,2-difluoro-2-(fluorosulfonyl)acetate in the presence of a  
metal catalyst such as copper iodide at a temperature range  
of from 0 to 150°C for 0.5 to 120 hours in a benzene sol-  
vent such as toluene, an ether solvent such as tetrahydro-  
furan or an amide solvent such as N,N-dimethylformamide, or  
a mixed solvent thereof.

[Preparation process-27]

Conversion of a nitrile group into a tetrazole group

When the compound of the formula (I) has a nitrile  
group as a substituent, it can be converted into the com-  
pound of the formula (I) having a tetrazole group by react-  
ing the former with sodium azide or trimethylsilyl azide at  
0 to 170°C in the presence of trimethylaluminum or di-n-  
butyltin oxide in a benzene solvent such as benzene or  
toluene.

[Preparation process-28]

Conversion of an amidino group into an alkoxycarbonylam-  
idino group

When the compound of the formula (I) contains an am-  
idino group, it can be converted into the compound of the  
formula (I) containing an alkoxycarbonylamidino group by

reacting the former with a reagent, for example, an acid chloride such as alkyl chlorocarbonate or alkyl p-nitrobenzylcarbonate at -78 to 100°C in the presence of a base in an alkyl halide solvent such as dichloromethane or chloroform, an amide solvent such as N,N-dimethylformamide or an ether solvent such as tetrahydrofuran.

Examples of the base include sodium carbonate, potassium carbonate, pyridine, 2,6-lutidine, 4-dimethylaminopyridine, diazabicyclo[5.4.0]undec-7-en (DBU).

[Preparation Process-29]

The sulfonyl derivative of the formula (I) having a primary or secondary amine on  $Q^1$ ,  $Q^2$ ,  $Q^3$ ,  $Q^4$  or  $T^1$  or a substituent substitutable therefor can be hydroxylated in a conventional manner.

For example, a sulfonyl derivative having a hydroxylated nitrogen atom can be obtained reacting the sulfonyl derivative of the formula (I) with a peroxide such as meta-chloroperbenzoic acid at -60 to 80°C, preferably -20 to 40°C, for 0.5 to 120 hours in a benzene solvent such as benzene, toluene or xylene, an ether solvent such as tetrahydrofuran or dimethoxyethane or an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride.

Alternatively, a sulfonyl derivative having a hydroxylated nitrogen atom can be obtained, for example, by reacting the sulfonyl derivative of the formula (I) with a peroxide such as benzoyl peroxide at -60 to 80°C, preferably -



20 to 40°C, for 0.5 to 120 hours in a benzene solvent such as benzene, toluene or xylene, an ether solvent such as dimethoxyethane or an alkyl halide solvent such as dichloromethane, chloroform or carbon tetrachloride, thereby obtaining a sulfonyl derivative having a benzoyloxy-  
5 nitrogen atom; and then subjecting the resulting sulfonyl derivative having a benzoyloxy-  
nitrogen atom to hydrolysis in accordance with the process as described in [Preparation Process-19].

10 The sulfonyl derivative of the formula (I) according to the present invention, salt thereof or solvate thereof has peculiar and excellent FXa inhibitory activity and is therefore useful as a coagulation suppressor or a preventive and/or remedy for thrombosis or embolism.

15 Accordingly, the sulfonyl derivative of the present invention can treat or prevent various diseases caused by thrombosis or embolism, for example, cerebral infarction, cerebral embolism, myocardial infarction, pulmonary infarction, pulmonary embolism, Buerger's disease, deep vein  
20 thrombosis and disseminated intravascular coagulation syndrome, thrombus formation after valve replacement, reocclusion after revascularization and formation of thrombus upon extracorporeal circulation, without acting on platelets.

25 The sulfonyl derivative of the present invention exhibits effects even by the oral administration so that it can be administered either orally or parenterally. Upon

administration, it can be formulated as a pharmaceutical composition comprising the sulfonyl derivative and a pharmaceutically acceptable carrier. The dose of the sulfonyl derivative can be changed as needed depending on the symptom, age, weight and/or the like of a patient. It is necessary to administer the derivative in an amount of 1 to 1000 mg/day, preferably 5 to 300 mg/day per adult. Although no particular limitation is imposed on the dosage form, examples include tablets, capsules, powders, granules, suspensions, syrups and dry syrups. The derivative together with ordinarily employed additives such as excipient, lubricant or binder can be formulated into the above-described dosage forms in accordance with the known formulation technique.

No particular limitation is imposed on the dosage form in the case of parenteral administration but examples include ointments, plasters, injections and suppositories. As an injection, the derivative may be administered subcutaneously or intravenously or by intravenous drip in an amount of 0.1 to 100 mg/day, preferably 0.5 to 30 mg/day per adult.

### **Examples**

The present invention will hereinafter be described more specifically by Referential Examples, Examples and Tests. It should however be borne in mind that the present invention is not limited to or by them.

Some of the starting material compounds used for preparing the sulfonyl derivative of the present invention are novel compounds. These compounds and preparation process therefor will be described in Referential Examples.

5        Upon preparation of the compound, Merck Silica Gel 60 or Yamazen Silica Gel for moderate pressure liquid chromatography were employed for silica gel column chromatography.

10        In the nuclear magnetic resonance spectrum (NMR), tetramethylsilane was used as an internal standard.

[Referential Example 1] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride and trifluoroacetate

15        In dichloromethane (20 ml), tert-butyl 1-piperazine carboxylate (856 mg) was dissolved. To the resulting solution, triethylamine (0.77 ml) and 6-chloro-2-naphthylsulfonyl chloride (WO96/10022) (1.20 g) were added, followed by stirring at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting  
20        mixture was washed with 1N hydrochloric acid. The organic layer extracted was dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was dissolved in saturated hydrochloride in ethanol (10 ml), followed by concentration under reduced  
25        pressure and washing with ethyl acetate, whereby the hydrochloride (1.62 g, quant.) of the title compound was ob-

tained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.1-3.4 (8H, m), 7.75 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.86 (1H, dd,  $J=8.8, 1.5\text{Hz}$ ), 8.22 (1H, d,  $J=8.8\text{Hz}$ ), 8.26-8.32 (2H, m), 8.56 (1H, s), 8.63 (2H, br s).

5 MS (FAB)  $m/z$ : 311  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 313  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}\cdot\text{HCl}\cdot 0.1\text{H}_2\text{O}$

Calculated: C, 48.17; H, 4.68, Cl, 20.31; N, 8.03; S, 9.19.

Found: C, 47.91; H, 4.68; Cl, 20.41; N, 7.80; S, 9.21.

10 Instead of the saturated solution hydrochloride in ethanol, treatment was carried out using trifluoroacetic acid, whereby the trifluoroacetate was obtained.

Elementary analysis for  $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}\cdot\text{CF}_3\text{CO}_2\text{H}$

Calculated: C, 45.24; H, 3.80, Cl, 8.35; F, 13.42; N, 6.59; S, 7.55.

15 Found: C, 44.84; H, 3.80; Cl, 8.27; F, 13.72; N, 6.29; S, 7.50.

[Referential Example 2] 4-(4-Pridyl)benzoic acid hydrochloride

20 At room temperature, 4-bromopyridine hydrochloride (11.7 g) and 4-carboxyphenylboronic acid (10.0 g) were dissolved in toluene (250 ml) and water (250 ml). To the resulting solution, tetrakis(triphenylphosphine)palladium (0) (5.00 g) and anhydrous sodium carbonate (25.4 g) were added successively, followed by refluxing under heat at  $120^\circ\text{C}$  for

25 19 hours. After allowed to cool down to room temperature,

the reaction mixture was added with ethyl acetate and water, whereby the water layer was separated. The organic layer was extracted twice with water. All the water layers so obtained were combined and to the resulting solution, concentrated hydrochloric acid was added to make it acidic, followed by washing with ethyl acetate again. The solvent was distilled off from the water layer until it decreased to 100 ml. The colorless solid so precipitated was collected by filtration and dried under reduced pressure, whereby the title compound (8.37 g, 59%) was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 8.11 (2H, d,  $J=8.8\text{Hz}$ ), 8.14 (2H, d,  $J=8.8\text{Hz}$ ), 8.35 (2H, d,  $J=6.6\text{Hz}$ ), 8.97 (2H, d,  $J=6.6\text{Hz}$ ).

Elementary analysis for  $\text{C}_{12}\text{H}_9\text{NO}_2 \cdot \text{HCl} \cdot 0.3\text{H}_2\text{O}$

Calculated: C, 59.79; H, 4.43, N, 5.81

Found: C, 59.87; H, 4.35; N, 5.53.

MS (FAB)  $m/z$ : 200 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 3] 1-tert-Butoxycarbonyl-4-[4-(4-pyridyl)benzoyl]piperazine

In N,N-dimethylformamide (40 ml), 4-(4-pyridyl)benzoic acid hydrochloride (654 mg) and tert-butyl 1-piperazinecarboxylate (569 mg) were suspended. To the resulting suspension, 1-hydroxybenzotriazole (374 mg) and N-methylmorpholine (336  $\mu\text{l}$ ) were added. The resulting mixture was ice cooled, followed by the addition of 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (796

mg). After stirring at room temperature for 7 hours, the solvent was distilled off. The residue was purified by chromatography on a silica gel column (2% methanol - dichloromethane), followed by washing with hexane, whereby the title compound (905 mg, 89%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48 (9H, s), 3.40-3.91 (8H, m), 7.51 (2H, d,  $J=5.9\text{Hz}$ ), 7.53 (2H, d,  $J=8.1\text{Hz}$ ), 7.69 (2H, d,  $J=8.1\text{Hz}$ ), 8.69 (2H, d,  $J=5.9\text{Hz}$ ).

Elementary analysis for  $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3$

Calculated: C, 68.64; H, 6.86, N, 11.44.

Found: C, 68.48; H, 6.84; N, 11.17.

[Referential Example 4] 1-[4-(4-Pyridyl)benzoyl]piperazine ditrifluoroacetate

In dichloromethane (30 ml), 1-tert-butoxycarbonyl-4-[4-(4-pyridyl)benzoyl]piperazine (944 mg) was dissolved. Under ice cooling, trifluoroacetic acid (30 ml) was added to the resulting solution, followed by stirring at room temperature for one hour. The solvent was distilled off. Tetrahydrofuran was added to the residue to solidify the same, whereby the title compound (1.28 g, 100%) was obtained as a colorless amorphous solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.1-3.3 (4H, br s), 3.5-4.0 (4H, m), 7.65 (2H, d,  $J=7.8\text{Hz}$ ), 7.95-8.05 (4H, m), 8.79 (2H, d,  $J=5.4\text{Hz}$ ), 8.95-9.10 (1H, br s)

[Referential Example 5] 4-tert-Butoxycarbonyl-2-

ethoxycarbonyl-1-[4-(4-pyridyl)benzoyl]piperazine

In toluene (150 ml), 1,2-dibromopropionic acid (58.0 g) was dissolved. To the resulting solution, a solution of N,N'-dibenzylethylenediamine (53.5 g) and triethylamine (53 ml) in toluene (toluene: 50 ml) was added dropwise under ice cooling. Toluene (100 ml) was added again to the reaction mixture, followed by stirring at room temperature for 14 hours, addition of toluene (100 ml) again and stirring at 60 to 80°C for 4 hours. The insoluble matter was filtered off. The filtrate was washed with water and dried over anhydrous potassium carbonate. The solvent was then distilled off under reduced pressure. The residue was dissolved in acetic acid (200 ml). To the resulting solution, 10% palladium carbon (water content: about 50%, 40 g) was added, followed by catalytic reduction under 4 atmospheric pressure for 4 hours. The catalyst was filtered off and the filtrate was distilled off under reduced pressure. To the residue, dichloromethane and a saturated aqueous solution of potassium carbonate were added to separate the organic layer, followed by drying over anhydrous potassium carbonate. The solvent was distilled off under reduced pressure. The residue was dissolved in dichloromethane (350 ml), followed by the addition of 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (46.5 g) under ice cooling. The reaction mixture was heated gradually to room temperature, at which stirring was conducted for 14

hours. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 2% methanol - dichloromethane), whereby 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperazine (5.82 g, 10%) was obtained.

In the same manner as in Referential Example 3, the a reaction was conducted using the resulting product and 4-(4-pyridyl)benzoic acid hydrochloride as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.2-1.4 (3H,m), 1.46 (9H,s), 2.7-5.4 (7H,m), 7.51 (2H,d,J=5.2Hz), 7.59 (2H,d,J=7.6Hz), 7.69 (2H,d,J=7.6Hz), 8.69 (2H,d,J=5.2Hz).

MS (FAB)  $m/z$ : 440 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 6] 6-(4-Pyridyl)nicotinic acid hydrochloride

In tetrahydrofuran (20 ml), 6-chloronicotinic acid (535 mg) and diethyl (4-pyridyl)borane (Chem. Pharm. Bull., 33, 4755, 1985) (500 mg) were dissolved. To the resulting solution, tetrabutylammonium bromide (546 mg), potassium hydrochloride (570 mg), tetrakis(triphenylphosphine) palladium (0) (392 mg) and water (0.5 ml) were added under an argon atmosphere, followed by heating under reflux for 6 hours. Dilute hydrochloric acid was added to the reaction mixture to make it acidic. Water and ethyl acetate were poured into the resulting mixture for extraction. The wa-



ter layer so extracted was distilled off under reduced pressure. The residue was purified by chromatography through a synthetic adsorbent ("Diaion® HP-20", water ~ 50% acetonitrile - water). To the resulting fraction, dilute  
5 hydrochloric acid was added to make it acidic. The solvent was then distilled off. Tetrahydrofuran was added to the residue and the precipitate was collected by filtration, whereby the title compound (269 mg, 32%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 8.45-8.55(2H,m), 8.65(2H,d,J=6.8Hz),

10 9.03(2H,d,J=6.8Hz), 9.27(1H,s).

MS (FAB)  $m/z$ : 201 ( $\text{M}+\text{H}$ ) $^+$

[Referential Example 7] Methyl 4-(3-pyridyl)benzoate

In tetrahydrofuran (100 ml), methyl 4-bromobenzoate (5.04 g) and diethyl-3-pyridylborane (Chem. Pharm. Bull.,  
15 33, 4755, 1985) (2.30 g) were dissolved, followed by the addition of tetrabutylammonium bromide (2.51 g), potassium hydroxide (2.63 g), tetrakis(triphenylphosphine)palladium (0) (1.8 g) and water (1 ml) under an argon atmosphere. The resulting mixture was heated under reflux for 2 hours.  
20 After ice cooling, an aqueous ammonium chloride solution and ethyl acetate were added to the reaction mixture. The organic layer so separated was dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent was purified by chromatography on a silica gel column (hexane: ethyl acetate = 1:1). The solvent was then  
25

distilled off. To the residue, methanol and 1N aqueous hydrochloric acid in ethanol were added. The solvent was distilled off again. Tetrahydrofuran was added to the residue and the solid so precipitated was collected by filtration. After drying, the title compound (1.76 g, 45%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.91(3H,s), 8.0-8.1(3H,m), 8.1-8.15(2H,m), 8.75-8.85(1H,m), 8.85-8.95(1H,m), 9.25-9.3(1H,m).

[Referential Example 8] 4-(3-Pyridyl)benzoic acid hydrochloride

At room temperature, methyl 4-(3-pyridyl)benzoate (1.76 g) was dissolved in a mixed solvent of 1N hydrochloric acid (50 ml) and dioxane (50 ml), followed by heating under reflux for 4 hours. The solvent was then distilled off under reduced pressure. Tetrahydrofuran was added to the residue, followed by washing, whereby the title compound (1.55 g, 93%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 7.95-8.0(3H,m), 8.10(2H,d,J=8.3Hz), 8.65-8.75(1H,m), 8.8-8.9(1H,m), 9.22(1H,d,J=2.0Hz)

[Referential Example 9] Methyl 4-(2-aminopyridin-5-yl)benzoate

In the same manner as in Example 2, a reaction was conducted using 5-bromo-2-aminopyridine and 4-carboxyphenylboronic acid as starting materials, whereby 4-

(2-aminopyridin-5-yl)benzoic acid was obtained.

The resulting 4-(2-aminopyridin-5-yl)benzoic acid (684 mg) was dissolved in methanol (50 ml) at room temperature, followed by the addition of concentrated sulfuric acid (1 ml). After heating under reflux for 2 hours, the reaction mixture was made weakly alkaline with an aqueous solution of sodium bicarbonate. Water and ethyl acetate were added to the resulting mixture to separate the organic layer. The organic layer was then dried over anhydrous magnesium sulfate. The solvent was distilled off. Hexane was added to the residue for crystallization, whereby the title compound (243 mg, 23%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.94 (3H, s), 4.57 (2H, br s), 6.60 (1H, d,  $J=8.8\text{Hz}$ ), 7.58 (2H, d,  $J=8.8\text{Hz}$ ), 7.72 (1H, dd,  $J=8.8, 2.4\text{Hz}$ ), 8.09 (2H, d,  $J=8.8\text{Hz}$ ), 8.38 (1H, d,  $J=2.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 229 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$

Calculated: C, 68.41; H, 5.30, N, 12.27.

Found: C, 68.78; H, 5.45; N, 12.09.

[Referential Example 10] Methyl 4-[2-(tert-Butoxycarbonylamino)pyridin-5-yl]benzoate

At room temperature, methyl 4-(2-aminopyridin-5-yl)benzoate (200 mg) was suspended in tert-butanol (20 ml). To the resulting suspension, di-tert-butyl dicarbonate (286

mg) was added and the resulting mixture was stirred for 24 hours. After the solvent was distilled off, the residue was purified by chromatography on a silica gel column (1% methanol - dichloromethane), whereby the title compound  
5 (155 mg, 54%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.55(9H,s), 3.95(3H,s),  
7.63(2H,d,J=8.3Hz), 7.92(1H,dd,J=8.8,2.4Hz),  
8.07(1H,d,J=8.8Hz), 8.09(1H,br s), 8.12(2H,d,J=8.3Hz),  
8.55(1H,d,J=2.4Hz).

10 MS(FAB)  $m/z$ : 329 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$

Calculated: C, 65.84; H, 6.14, N, 8.53;

Found: C, 65.67; H, 6.02; N, 8.40.

[Referential Example 11] 4-[2-(tert-

15 Butoxycarbonylamino)pyridin-5-yl]benzoic acid

At room temperature, methyl 4-[2-(tert-  
butoxycarbonylamino)pyridin-5-yl]benzoate (250 mg) was sus-  
pended in a mixed solvent of tetrahydrofuran (10 ml) and  
methanol (10 ml), followed by the addition of a 1N aqueous  
20 sodium hydroxide solution (8 ml). The resulting mixture  
was stirred for 5 hours. The reaction mixture was made  
weakly acidic with an aqueous citric acid solution, fol-  
lowed by the addition of saturated saline and n-butanol to  
separate the organic layer. The organic layer was then  
25 dried over anhydrous magnesium sulfate. The solvent was

distilled off, whereby the title compound (120 mg, 49%) was obtained as a crude purified product.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.49 (9H, s), 7.83 (2H, d,  $J=8.3\text{Hz}$ ),  
7.91 (1H, d,  $J=8.8\text{Hz}$ ), 8.02 (2H, d,  $J=8.3\text{Hz}$ ),  
5 8.13 (1H, dd,  $J=8.8, 2.4\text{Hz}$ ), 8.65 (1H, d,  $J=2.4\text{Hz}$ ), 9.95 (1H, s),  
12.99 (1H, br s).

[Referential Example 12] 1-[4-[2-(tert-butoxycarbonylamino)pyridin-5-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

10 In a mixed solvent of dichloromethane (20 ml) and N,N-dimethylformamide (1 ml), 4-[2-(tert-butoxycarbonyl)amino]pyridin-5-yl]benzoic acid (74 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (110 mg) were suspended. To the resulting suspen-  
15 sion, 1-hydroxybenzotriazole (35 mg) and N-methylmorpholine (34  $\mu\text{l}$ ) were added, followed by the addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (68 mg) under ice cooling. After stirring at room temperature for 6 hours, the solvent was distilled off. The residue  
20 was purified by chromatography on a silica gel column (1% methanol - dichloromethane). The solvent was then distilled off, whereby the title compound (128 mg, 90%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.54 (9H, s), 3.00-3.30 (4H, m), 3.50-  
25 4.10 (4H, m), 7.39 (2H, d,  $J=7.8\text{Hz}$ ), 7.54 (2H, d,  $J=7.8\text{Hz}$ ),

7.60 (1H, dd, J=8, 8, 2.0Hz), 7.71 (1H, dd, J=8.8, 1.5Hz),  
 7.84 (1H, dd, J=8.8, 2.4Hz), 7.88 (1H, br s), 7.9-8.0 (3H, m),  
 8.03 (1H, d, J=8.8Hz), 8.31 (1H, s), 8.46 (1H, d, J=2.4Hz).

[Referential Example 13] 4-(4-Aminophenyl)benzoic acid hy-  
 5 drochloride

In the same manner as in Referential Example 2, a re-  
 action was conducted using 4-bromoaniline and 4-  
 carboxyphenylboronic acid as starting materials, whereby  
 the title compound was obtained.

10  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 7.31 (2H, d, J=7.3Hz), 7.75-7.85 (4H, m),  
 8.09 (2H, d, J=8.3Hz).

MS (FAB)  $m/z$ : 228 (M+H) $^+$ .

Elementary analysis for  $\text{C}_{13}\text{H}_{11}\text{NO}_2 \cdot \text{HCl}$

Calculated: C, 62.53; H, 4.84, N, 5.61; Cl, 14.20.

15 Found: C, 62.33; H, 4.83; N, 5.50; Cl, 14.14.

[Referential Example 14] Methyl 4-[4-(tert-  
 butoxycarbonylamino)phenyl]benzoate

In the same manner as in Referential Example 9 or 10,  
 a reaction was conducted using 4-(4-aminophenyl)benzoic  
 20 acid hydrochloride as a starting material, whereby the ti-  
 tle compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.54 (9H, s), 3.94 (3H, s), 6.56 (1H, br s),  
 7.46 (2H, d, J=8.8Hz), 7.57 (2H, d, J=8.8Hz), 7.63 (2H, d, J=8.3Hz),  
 8.08 (2H, d, J=8.3Hz).

25 MS (FAB)  $m/z$ : 328 (M+H) $^+$ .

Elementary analysis for  $C_{19}H_{21}NO_4$

Calculated: C, 69.71; H, 6.47, N, 4.28.

Found: C, 69.49; H, 6.44; N, 4.42.

[Referential Example 15] 4-[4-(tert-butoxycarbonylamino)phenyl]benzoic acid

In the same manner as in Referential Example 11, a reaction was conducted using methyl 4-[4-(tert-butoxycarbonylamino)phenyl]benzoate (501 mg), whereby the title compound (426 mg, 89%) was obtained.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.54(9H,s), 6.57(1H,br s), 7.47(2H,d,J=8.3Hz), 7.59(2H,d,J=8.3Hz), 7.66(2H,d,J=8.3Hz), 8.13(2H,d,J=8.3Hz).

MS (FAB)  $m/z$ : 314 ( $M+H$ ) $^+$ .

Elementary analysis for  $C_{18}H_{19}NO_4$

Calculated: C, 68.99; H, 6.11, N, 4.47.

Found: C, 68.91; H, 6.27; N, 4.24.

[Referential Example 16] 1-[4-[4-(tert-butoxycarbonylamino)phenyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-[4-(tert-butoxycarbonylamino)phenyl]benzoic acid (150 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (203 mg) as starting materials, whereby the title compound

(303 mg, 100%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.53(9H,s), 2.90-3.30(4H,m), 3.50-4.10(4H,m), 6.56(1H,s), 7.35(2H,d,J=8.3Hz), 7.44(2H,d,J=8.3Hz), 7.49(2H,d,J=8.3Hz), 7.54(2H,d,J=8.3Hz), 7.59(1H,dd,J=8.8,2.0Hz), 7.76(1H,dd,J=8.8,2.0Hz), 7.90-7.95(3H,m), 8.30(1H,br s).

[Referential Example 17] Methyl 4-acetylbenzoate

In a mixed solvent of tetrahydrofuran (100 ml) and methanol (7 ml), methyl 4-acetylbenzoate (3.28 g) was dissolved at room temperature, followed by the addition of trimethylsilyldiazomethane (a 2.0M hexane solution, 12 ml) in portions under ice cooling. After heating to room temperature and stirring for 30 minutes, the solvent was distilled off. To the residue, an aqueous solution of sodium bicarbonate and ether were added. The organic layer so separated was dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was crystallized from hexane, whereby the title compound (2.90 g, 82%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.65(3H,s), 3.96(3H,s), 8.01(2H,d,J=8.3Hz), 8.13(2H,d,J=8.3Hz).  
MS (EI)  $m/z$ : 178 $\text{M}^+$ .

Elementary analysis for  $\text{C}_{10}\text{H}_{10}\text{O}_3$

Calculated: C, 67.41; H, 5.66.

Found: C, 67.28; H, 5.53.

[Referential Example 18] Methyl 4-bromoacetylbenzoate



At 15°C, methyl 4-acetylbenzoate (2.23 g) was dissolved in a hydrobromic acid acetic acid solution (30%, 10 ml). Bromine was gradually added dropwise to the reaction mixture to maintain its temperature at 15°C. After stirring for 10 minutes, the reaction mixture was cooled to 4°C. A mixed solvent of methanol (50 ml) and water (50 ml) was added to the reaction mixture for crystallization, followed by washing with hexane. By the collection through filtration, the title compound (2.29 g, 71%) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.96(3H,s), 4.47(2H,s),

8.05(2H,d,J=8.8Hz), 8.16(2H,d,J=8.8Hz).

MS (FAB)  $m/z$ : 257 [ $(\text{M}+\text{H})^+$ ,  $^{79}\text{Br}$ ], 259 [ $(\text{M}+\text{H})^+$ ,  $^{81}\text{Br}$ ].

Elementary analysis for  $\text{C}_{10}\text{H}_9\text{BrO}_3$

Calculated: C, 46.72; H, 3.53.

Found: C, 46.36; H, 3.63.

[Referential Example 19] Methyl 4-(2-aminothiazol-4-yl)benzoate

At room temperature, methyl 4-bromoacetylbenzoate (1.00 g) and thiourea (296 mg) were dissolved in isopropanol (100 ml), followed by heating under reflux for 15 minutes. Under stirring at the same temperature, anhydrous sodium carbonate (206 mg) was added to the reaction mixture. The resulting mixture was heated under reflux for 20 minutes. After completion of the reaction, water (50 ml)

was added under ice cooling and the solid so precipitated was collected by filtration. The solid was dissolved in water and dichloromethane. The organic layer so separated was dried over anhydrous sodium sulfate. The solvent was then distilled off. The pale yellow solid so precipitated was washed with ether, whereby the title compound (634 mg, 70%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.93(3H,s), 4.96(2H,br s), 6.88(1H,s), 7.85(2H,d,J=8.8Hz), 8.05(2H,d,J=8.8Hz).

MS (FAB)  $m/z$ : 235 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 20] 4-(2-Aminothiazol-4-yl)benzoic acid

At room temperature, methyl 4-(2-aminothiazol-4-yl)benzoate (300 mg) was suspended in a mixed solvent of tetrahydrofuran (5 ml) and methanol (5 ml), followed by the addition of a 1N aqueous sodium hydroxide solution (10 ml). The resulting mixture was stirred for one hour. To the reaction mixture, N,N-dimethylformamide (5 ml) was added, followed by heating under reflux for 6 hours. After completion of the reaction, the solvent was distilled off. To the residue, water and 1N hydrochloric acid were added successively and the pale yellow solid so precipitated was collected by filtration, whereby the title compound (229 mg, 69%) was obtained as a pale yellow solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 7.30(1H,br s), 7.87(2H,d,J=8.3Hz),

7.95-8.00 (2H,m).

MS (FAB)  $m/z$ : 221 (M+H)<sup>+</sup>.

Elementary analysis for  $C_{10}H_8N_2O_2S \cdot 0.75HCl \cdot 0.6H_2O$

Calculated: C, 46.48; H, 3.88, N, 10.84; Cl, 10.29; S,  
5 12.41.

Found: C, 46.36; H, 4.12, N, 10.64; Cl, 10.05; S,  
12.33.

[Referential Example 21] Methyl 4-(imidazol-4-yl)benzoate

At room temperature, methyl 4-bromoacetylbenzoate (2  
10 g) was dissolved in formamide (100 ml), followed by stir-  
ring at 180°C for 90 minutes. After completion of the re-  
action, the reaction mixture was ice cooled and dissolved  
in water and 1N hydrochloric acid. The resulting solution  
was purified by chromatography through a synthetic adsorb-  
15 ent ("Diaion HP-20", water ~ 50% acetonitrile - water).

The crude product so obtained was purified further by chro-  
matography on a silica gel column (5% methanol - dichlo-  
romethane), whereby the title compound (844 mg, 54%) was  
obtained as a pale yellow solid.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.93(3H,s), 7.46(1H,s), 7.75(1H,s),  
7.86(2H,m), 8.07(2H,d,J=8.3Hz).

MS (FAB)  $m/z$ : 203 (M+H)<sup>+</sup>.

[Referential Example 22] Methyl 4-[1-  
triphenylmethylimidazol-4(5)-yl]benzoate

25 Methyl 4-(imidazol-4-yl)benzoate (828 mg) was dis-

solved in dichloromethane (50 ml), followed by the addition of diisopropylethylamine (856  $\mu$ l) and triphenylmethyl chloride (1.37 g) under ice cooling. The resulting mixture was stirred at room temperature for 16 hours. The solvent was distilled off. The residue was purified by chromatography on a silica gel column (dichloromethane), whereby the title compound (1.08 g, 59%) was obtained as a colorless glassy solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.90 (3H, s), 7.15-7.22 (6H, m), 7.23 (1H, d,  $J=1.5\text{Hz}$ ), 7.30-7.40 (15H, m), 7.52 (1H, d,  $J=1.5\text{Hz}$ ), 7.79 (2H, d,  $J=8.3\text{Hz}$ ), 8.01 (2H, d,  $J=8.3\text{Hz}$ ).

MS (FAB)  $m/z$ : 445 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 23] 4-[1-Triphenylmethylimidazol-4(5)-yl]benzoic acid

At room temperature, methyl 4-[1-triphenylmethylimidazol-4(5)-yl]benzoate (1.04 g) was dissolved in a mixed solvent of tetrahydrofuran (10 ml) and methanol (10 ml). To the resulting solution, a 3N aqueous sodium hydroxide solution (6 ml) was added, followed by stirring for 5 hours. Tetrahydrofuran and methanol were removed by distillation under reduced pressure. An aqueous citric acid solution was added to the residue to make it weakly acidic, followed by the addition of water and dichloromethane. The organic layer so separated was washed with a saturated aqueous NaCl solution and dried over anhy-

drous sodium sulfate. The solvent was distilled off, whereby the title compound (1.13 g, quant.) was obtained as a crude purified product in the form of a colorless glassy solid.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.15-7.22 (6H, m), 7.23 (1H, d,  $J=1.5\text{Hz}$ ), 7.30-7.40 (9H, m), 7.69 (1H, d,  $J=1.5\text{Hz}$ ), 7.81 (2H, d,  $J=8.3\text{Hz}$ ), 8.10 (2H, d,  $J=8.3\text{Hz}$ ).

[Referential Example 24] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-4-[4-[1-triphenylmethyylimidazol-4(5)-yl]benzoyl]piperazine  
10

In the same manner as in Referential Example 12, a reaction was conducted by using 4-[1-triphenylmethyylimidazol-4(5)-yl]benzoic acid (371 mg) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (300 mg) as starting  
15 materials, whereby the title compound (560 mg, 90%) was obtained in the form of a colorless glassy solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.90-3.30 (4H, m), 3.50-4.10 (4H, m), 7.15-7.20 (6H, m), 7.28 (2H, d,  $J=8.3\text{Hz}$ ), 7.30-7.40 (9H, m), 7.49 (1H, d,  $J=1.0\text{Hz}$ ), 7.59 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
20 7.71 (2H, d,  $J=8.3\text{Hz}$ ), 7.75 (1H, dd,  $J=8.8, 1.5\text{Hz}$ ), 7.90-7.95 (3H, m), 8.29 (1H, br s).

MS (FAB)  $m/z$ : 723 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 25] 4-[2-Aminoimidazol-4-yl]benzoic acid hydrochloride

25 At room temperature, methyl 4-bromoacetylbenzoate

(1.37 g) and acetylguanidine (1.62 g) were suspended in acetonitrile, followed by heating under reflux for 16 hours. The solvent was then distilled off under reduced pressure. Water was added to the residue. The insoluble matter so precipitated was collected by filtration, followed by washing with ethanol, whereby methyl 4-[2-aminoimidazol-4-yl]benzoate was obtained. The resulting product was dissolved in a mixed solvent of dioxane (10 ml) and 1N hydrochloric acid (10 ml), followed by heating under reflux for 8 hours. The residue obtained by distilling off the solvent was solidified by tetrahydrofuran and then collected by filtration, whereby the title compound (500 mg, 39%) was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 7.55-7.65 (3H,m), 7.80 (2H,d,J=8.3Hz), 7.98 (2H,d,J=8.3Hz), 12.2-13.3 (3H,m).

MS (FAB)  $m/z$ : 204 ( $M+H$ ) $^+$ .

Elementary analysis for  $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$

Calculated: C, 48.30; H, 4.46; N, 16.90; Cl, 14.26.

Found: C, 48.03; H, 4.10; N, 16.49; Cl, 14.12.

[Referential Example 26] 1-[4-Bromo-2-(tert-butoxycarbonyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (200 ml), 4-bromophthalic anhydride (1.96 g) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride (3.00 g) were sus-

depended under ice cooling. To the resulting suspension, di-  
 isopropylethylamine (3.76 ml) was added, followed by stir-  
 ring for 20 minutes. To the reaction mixture, dilute hy-  
 drochloric acid and dichloromethane were added. The or-  
 5 ganic layer so separated was dried over anhydrous sodium  
 sulfate. The solvent was concentrated so that the volume  
 was reduced to 200 ml. To the concentrate, N,N'-  
 diisopropyl-O-tert-butylisourea (2.6 g) was added under ice  
 cooling and the resulting mixture was stirred at room tem-  
 10 perature for 3 days. Dilute hydrochloric acid and dichlo-  
 romethane were added to the reaction mixture. The organic  
 layer so separated was dried over anhydrous sodium sulfate.  
 The residue was purified by chromatography on a silica gel  
 column (hexane : ethyl acetate = 3:1 ~ 1:1), whereby the  
 15 title compound (1.78 g, 35%) was obtained as a colorless  
 solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.30(9H,s), 2.90-3.40(6H,m), 3.80-  
 4.00(2H,m), 7.01(1H,d,J=8.3Hz), 7.59(1H,dd,J=8.3,2.0Hz),  
 7.61(1H,dd,J=8.3,2.0Hz), 7.76(1H,dd,J=8.8,2.0Hz),  
 20 7.85-7.95(3H,m), 8.00(1H,d,J=2.0Hz), 8.29(1H,br s).  
 [Referential Example 27] 1-[2-tert-Butoxycarbonyl-4-  
 (pyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-  
 yl)sulfonyl]piperazine hydrochloride

In the same manner as in Referential Example 7, a re-  
 25 action was conducted using 1-[4-bromo-2-(tert-

butoxycarbonyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine and diethyl(4-pyridyl)borane as starting materials, whereby the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.37(9H,s), 2.80-3.50(6H,m), 3.80-4.00(2H,m), 7.40(1H,d,J=7.8Hz), 7.60(1H,dd,J=8.8,2.0Hz), 7.77(1H,dd,J=8.3,1.5Hz), 7.87(1H,dd,J=7.8,2.0Hz), 7.90-7.95(3H,m), 8.10(2H,d,J=6.8Hz), 8.25(1H,d,J=2.0Hz), 8.31(1H,br s), 8.90(2H,d,J=6.8Hz).

10 MS (FAB)  $m/z$ : 592 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{31}\text{H}_{30}\text{ClN}_3\text{O}_5\text{S}\cdot\text{HCl}\cdot 0.2\text{H}_2\text{O}\cdot\text{THF}$

Calculated: C, 59.69; H, 5.64; N, 5.97; Cl, 10.07; S, 4.55.

Found: C, 59.55; H, 5.45; N, 5.87; Cl, 9.97; S, 4.68.

[Referential Example 28] 5-(4-Pyridyl)thiophene-2-

15 carboxylic acid hydrochloride

In the same manner as in Referential Example 6, a reaction was conducted using 5-bromothiophene-2-carboxylic acid and diethyl (4-pyridyl)borane as starting materials, whereby the title compound was obtained.

20  $^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ : 7.87(1H,d,J=3.9Hz), 8.17(1H,d,J=3.9Hz), 8.29(2H,d,J=6.8Hz), 8.88(2H,d,J=6.8Hz).

MS (FAB)  $m/z$ : 206 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{10}\text{H}_7\text{NO}_2\text{S}\cdot\text{HCl}\cdot 0.8\text{H}_2\text{O}$

Calculated: C, 46.90; H, 3.78; N, 5.47; Cl, 13.84; S,

25 12.52.



Found: C, 46.77; H, 3.76; N, 5.27; Cl, 13.83; S, 12.56.

[Referential Example 29] 5-(4-Pyridyl)furan-2-carboxylic acid hydrochloride

5 In the same manner as in Referential Example 6, a reaction was conducted using 5-bromofuran-2-carboxylic acid and diethyl (4-pyridyl)borane as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.49(1H,d,J=3.4Hz), 7.80-7.90(1H,m), 8.20-8.30(2H,m), 8.85-8.95(2H,m).

10 [Referential Example 30] 4-(2-Pyridyl)benzoic acid hydrochloride

To water (200 ml), 2-(p-tolyl)pyridine (17.2 g) was added. To the resulting mixture, potassium permanganate (21.0 g) was added, followed by heating under reflux for 18 hours. After the precipitate was filtered off, dichloromethane was added to the filtrate to separate the water layer. The water layer was then made acidic with 2N hydrochloric acid. The acidic aqueous solution was concentrated. The precipitate was collected by filtration, followed by washing with water and ethyl acetate, whereby the title compound (7.07 g, 35%) was obtained as a white solid.

20 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.60(1H,t,J=5.9Hz), 8.08(2H,d,J=7.8Hz), 8.17(2H,m), 8.21(2H,d,J=7.8Hz), 8.78(1H,d,J=4.9Hz).

25 MS (EI) m/z: 199M<sup>+</sup>.

[Referential Example 31] 1-[(E)-4-chlorostyrylsulfonyl)piperazine hydrochloride

In the same manner as in Referential Example 1, a reaction was conducted using tert-butyl 1-piperazinecarboxylate and (E)-4-chlorostyrylsulfonyl chloride as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.20 (4H, br s), 3.33-3.38 (4H, m), 7.47 (2H, s), 7.53 (1H, d,  $J=8.8\text{Hz}$ ), 7.82 (1H, d,  $J=8.8\text{Hz}$ ).

Elementary analysis for  $\text{C}_{12}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}\cdot\text{HCl}$

Calculated: C, 44.59; H, 4.99, Cl, 21.94; N, 8.67; S, 9.92.

Found: C, 44.42; H, 4.78, Cl, 21.83; N, 8.68; S, 9.87.

[Referential Example 32] 4-(2,4-Diamino-6-pyrimidyl)benzoic acid hydrochloride

In toluene (9 ml), 6-chloro-2,4-diaminopyrimidine (434 mg) was dissolved, followed by the addition of 4-carboxyphenylboronic acid (667 mg), ethanol (2.5 ml), sodium carbonate (635 mg), water (3.0 ml) and bis(triphenylphosphine)palladium (II) dichloride (65 mg). The resulting mixture was heated under reflux for 24 hours under an argon gas atmosphere. Ethyl acetate and water were added to the reaction mixture. The water layer so separated was made acidic with 2N hydrochloric acid. The insoluble matter was collected by filtration, washed with water and tetrahydrofuran and then dried, whereby the title

compound (371 mg, 54%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 6.43(1H,s), 7.30-7.80(2H,br),  
7.96(2H,d,J=7.8Hz), 8.12(2H,d,J=7.8Hz), 8.27(2H,br s),  
12.77(1H,br), 13.33(1H,br).

5 MS (EI)  $m/z$ : 230 $\text{M}^+$ .

Elementary analysis for  $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_2\text{S}\cdot 0.95\text{HCl}\cdot 1.9\text{H}_2\text{O}$

Calculated: C, 44.17; H, 4.97; Cl, 11.26; N, 18.73.

Found: C, 44.33; H, 4.97; Cl, 11.32; N, 18.65.

[Referential Example 33] 1-tert-Butoxycarbonyl-4-[4-(2-  
10 pyridyl)benzoyl]piperazine

In the same manner as in Referential Example 3, a re-  
action was conducted using 4-(2-pyridyl)benzoic acid hydro-  
chloride obtained in Referential Example 30 and tert-butyl  
1-piperazinecarboxylate as starting materials, whereby the  
15 title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47(9H,s), 3.43(4H,br), 3.51(2H,br),  
3.76(2H,br), 7.28(1H,d,J=5.9Hz), 7.52(2H,d,J=7.8Hz),  
7.76(1H,m), 7.79(1H,m), 8.05(2H,d,J=7.8Hz),  
8.71(1H,d,J=4.9).

20 MS (FAB)  $m/z$ : 368 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3\cdot 0.1\text{H}_2\text{O}$

Calculated: C, 68.31; H, 6.88; N, 11.38;

Found: C, 68.26; H, 6.86; N, 11.42.

[Referential Example 34] 2-[4-[[4-(tert-  
25 Butoxycarbonyl)piperazin-1-yl]carbonyl]phenyl]pyridine N-

oxide

At -10°C, metachloroperbenzoic acid (789 mg) was added to a solution of 1-tert-butoxycarbonyl-4-[4-(2-pyridyl)benzoyl]piperazine (517 mg) in dichloromethane (dichloromethane: 8 ml). The resulting mixture was stirred for 24 hours, followed by dilution with dichloromethane. A small amount of an aqueous sodium thiosulfate solution and a saturated aqueous NaCl solution were added to the dilute solution. The organic layer so separated was washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane : methanol = 20:1), whereby the title compound (415 mg, 77%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 1.48(9H,s), 3.47(6H,br), 3.76(2H,br), 7.29(1H,m), 7.34(1H,t,J=7.8Hz), 7.44(1H,dd,J=7.8,2.0Hz), 7.52(2H,d,J=7.8Hz), 7.90(2H,d,J=7.8Hz), 8.35(1H,d,J=5.9Hz).

MS (FAB)  $m/z$ : 384 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 35] 2-[4-[(1-Piperazinyl)carbonyl]phenyl]pyridine N-oxide hydrochloride

In dichloromethane (2.5 ml), 2-[4-[[4-(tert-butoxycarbonyl)piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide was dissolved. To the resulting solution, a satu-

rated solution of hydrochloride in ethanol (2.5 ml) was added, followed by stirring at room temperature for 1 hour. After the solvent was distilled off under reduced pressure, water was added to the residue, whereby an aqueous solution was obtained. Acetone was added to the aqueous solution until the solution became turbid. The precipitate was collected by filtration and washed with acetone, whereby the title compound (274 mg, 81%) was obtained.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 3.17(4H, br s), 3.50-3.95(4H, br), 7.43(1H, d,  $J=3.9\text{Hz}$ ), 7.44(1H, d,  $J=3.9\text{Hz}$ ), 7.57(2H, d,  $J=8.8\text{Hz}$ ), 7.66(1H, t,  $J=3.9\text{Hz}$ ), 7.92(2H, d,  $J=8.8\text{Hz}$ ), 8.36(1H, t,  $J=3.9\text{Hz}$ ), 9.21(2H, br).

MS (FAB)  $m/z$ : 284 ( $M+H$ ) $^+$ .

[Referential Example 36] 1-(tert-Butoxycarbonyl)-4-[4-(3-pyridyl)benzoyl]piperazine

In the same manner as in Referential Example 3, a reaction was conducted using 4-(3-pyridyl)benzoic acid hydrochloride obtained in Referential Example 8 and tert-butyl 1-piperazinecarboxylate as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47(9H, s), 3.35-3.85(8H, br), 7.38(1H, dd,  $J=7.8, 4.9\text{Hz}$ ), 7.52(2H, d,  $J=8.3\text{Hz}$ ), 7.63(2H, d,  $J=8.3\text{Hz}$ ), 7.88(1H, m), 8.62(1H, dd,  $J=1.5, 4.9\text{Hz}$ ), 8.84(1H, d,  $J=2.0\text{Hz}$ ).

[Referential Example 37] 3-[4-[[4-(tert-

Butoxycarbonyl)piperazin-1-yl]carbonyl]phenyl]pyridine N-oxide

In the same manner as in Referential Example 34, the title compound was obtained as a colorless solid by using  
 5 1-(tert-butoxycarbonyl)-4-[4-(3-pyridyl)benzoyl]piperazine as a starting material.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48 (9H, s), 3.35-4.83 (8H, br), 7.38 (1H, m), 7.47 (1H, m), 7.49-7.65 (4H, m), 8.23 (1H, dd,  $J=6.4, 1.5\text{Hz}$ ), 8.47 (1H, t,  $J=1.5\text{Hz}$ ).

10 MS (FAB)  $m/z$ : 384 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$

Calculated: C, 65.02; H, 6.63; N, 10.83.

Found: C, 65.30; H, 6.65; N, 10.43.

[Referential Example 38] 2-Hydroxy-4-(4-pyridyl)benzoic  
 15 acid

In water (22.5 ml) and a 47% aqueous solution of hydrobromic acid (22.5 ml), 4-amino-2-hydroxybenzoic acid (5.04 g) was dissolved. While the resulting solution mixture was maintained at  $5^\circ\text{C}$  or lower, an aqueous solution  
 20 (water: 15.0 ml) of sodium nitrite (2.26 g) was added dropwise thereto, followed by stirring for 30 minutes under ice cooling. The reaction mixture was added, in portions, to a solution of cuprous bromide (5.63 g) dissolved in a 47% aqueous solution of hydrobromic acid (15 ml) under ice  
 25 cooling. The resulting mixture was stirred at room tem-

perature for 150 minutes. Ethyl acetate was added to the reaction mixture for extraction. The organic layer so obtained was washed with water and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ 10% methanol - dichloromethane), whereby 4-bromo-2-hydroxybenzoic acid (5.51 g) was obtained as a crudely purified product.

The crudely purified product (298 mg) was reacted as in Referential Example 6, whereby the title compound (70 mg, 21%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 7.30-7.40 (2H, m), 7.78 (2H, d,  $J=4.4\text{Hz}$ ), 7.92 (1H, d,  $J=6.3\text{Hz}$ ), 8.69 (2H, d,  $J=5.9\text{Hz}$ ).

MS (FAB)  $m/z$ : 216 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 39] 4-Bromo-3-hydroxybenzoic acid

In acetic acid (24.5 ml), 3-hydroxybenzoic acid (5.00 g) was suspended. To the resulting suspension, a solution of bromine (1.9 ml) in acetic acid (acetic acid: 5 ml) was added dropwise under ice cooling, followed by stirring at room temperature for 33 hours. The reaction mixture was ice cooled. The crystals so precipitated were collected by filtration and then washed with acetic acid, whereby the title compound (1.68 g, 21%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 7.28 (1H, dd,  $J=7.8, 2.0\text{Hz}$ ), 7.51 (1H, d,  $J=2.0\text{Hz}$ ), 7.59 (1H, d,  $J=8.3\text{Hz}$ ), 10.54 (1H, br s),

12.84(1H,br).

[Referential Example 40] Methyl 4-bromo-3-methoxybenzoate

In the same manner as in Referential Example 17, a reaction was conducted using 4-bromo-3-hydroxybenzoic acid as a starting material, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.92(3H,s), 3.96(3H,s),  
7.51(1H,dd,J=8.3,2.0Hz), 7.55(1H,d,J=2.0Hz),  
7.61(1H,d,J=8.8Hz).

10 [Referential Example 41] 3-Methoxy-4-(4-pyridyl)benzoic acid

In the same manner as in Referential Example 7, a reaction was conducted using methyl 4-bromo-3-methoxybenzoate and diethyl (4-pyridyl)borane. The crude product so obtained was reacted as in Referential Example 8, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.93(3H,s), 7.65-7.75(3H,m),  
8.20(2H,d,J=5.4Hz), 8.94(2H,d,J=6.3Hz).  
MS (FAB)  $m/z$ : 230 ( $\text{M}+\text{H}$ ) $^+$ .

20 [Referential Example 42] 4-tert-Butoxycarbonyl-1-[(6-chloronaphthalen-2-yl)sulfonyl]-2-ethoxycarbonylpiperazine

In dichloromethane (18 ml), 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperazine (517 mg) and 6-chloro-2-naphthylsulfonyl chloride (588 mg) were dissolved under ice cooling. To the resulting solution, diisopropylethylamine

25



(0.59 ml) was added, followed by stirring at room temperature for 63 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby the title compound (688 mg, 71%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.05 (3H, t,  $J=7.1\text{Hz}$ ), 1.38 (9H, s), 2.80-4.70 (9H, m), 7.55 (1H, dd,  $J=8.6, 2.2\text{Hz}$ ), 7.77 (1H, dd,  $J=8.6, 1.7\text{Hz}$ ), 7.85-7.90 (3H, m), 8.33 (1H, s).

MS (FAB)  $m/z$ : 483  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 485  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 43] 4-tert-Butoxycarbonyl-2-ethoxycarbonyl-1-[4-(3-pyridyl)benzoyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-(3-pyridyl)benzoic acid and 1-tert-butoxycarbonyl-3-ethoxycarbonylpiperazine as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20-1.40 (3H, m), 1.46 (9H, s), 2.70-4.80 (8H, m), 5.35 (1H, br), 7.35-7.70 (5H, m), 7.85-7.95 (1H, m), 8.64 (2H, dd,  $J=4.6, 1.7\text{Hz}$ ), 8.86 (1H, s).

MS (FAB)  $m/z$ : 440  $(\text{M}+\text{H})^+$ .

[Referential Example 44] Methyl N-tert-butoxycarbonyltranexamate

To methanol (20 ml), thionyl chloride (1 ml) was added dropwise under ice cooling, followed by the addition of tranexamic acid (2.04 g). The resulting mixture was heated

under reflux for 3 hours. The residue obtained by distilling the reaction mixture under reduced pressure was pulverized in ether and then collected by filtration, whereby colorless crystals (2.31 g) were obtained.

5       The resulting crystals (2.10 g) were dissolved in dichloromethane (40 ml), followed by the addition of N-methylmorpholine (1.2 ml). To the resulting mixture, a solution of di-tert-butyl dicarbonate (2.51 g) in dichloromethane (dichloromethane: 3 ml) was added under ice cooling. The resulting mixture was stirred at room temperature  
10       for 18 hours. After diluted with dichloromethane, the reaction mixture was washed with water and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by  
15       chromatography on a silica gel column (hexane : ethyl acetate = 10:1 ~ 3:1), followed by recrystallization from a mixed solvent of hexane and ethyl acetate, whereby colorless crystals (2.09 g, 65%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.90-1.10 (2H,m), 1.40-1.60 (12H,m), 1.80-  
20       1.90 (2H,m), 2.00-2.10 (2H,m), 2.24 (1H,m), 2.98 (2H,m),  
3.66 (3H,s), 4.58 (1H,br).

Elementary analysis for  $\text{C}_{14}\text{H}_{25}\text{NO}_4$

Calculated: C, 61.97; H, 9.29; N, 5.16.

Found:       C, 62.15; H, 9.42; N, 5.12.

25       [Referential Example 45] trans-4-(N-tert-

Butoxycarbonylaminomethyl)cyclohexylmethanol

Methyl N-tert-butoxycarbonyltranexamate (1.00 g) was dissolved in a mixed solvent of tetrahydrofuran (10 ml) and methanol (2 ml). To the resulting solution, sodium borohy-  
 5 dride (0.44 g) was added under ice cooling, followed by stirring at room temperature for 24 hours. After the addition of water, the reaction mixture was concentrated under reduced pressure. Ethyl acetate and dilute hydrochloric acid were added to the concentrate. The organic layer so  
 10 separated was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column in repetition (first time; dichloromethane ~ di-  
 chloromethane : methanol = 20:1, second time; hexane :  
 15 ethyl acetate = 3:1), whereby colorless crystals (0.74 g, 82%) were obtained. A portion of the crystals was recrystallized from a mixed solvent of hexane and ethyl acetate, whereby colorless crystals were obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 0.90-1.10 (4H,m), 1.30-1.60 (12H,m), 1.80-  
 20 2.00 (4H,m), 2.98 (2H,m), 3.45 (2H,d,J=6.4Hz), 4.59 (1H,br).

Elementary analysis for  $\text{C}_{13}\text{H}_{25}\text{NO}_3$

Calculated: C, 64.17; H, 10.35, N, 5.76.

Found: C, 64.31; H, 10.03; N, 5.74.

[Referential Example 46] trans-4-(N-tert-  
 25 Butoxycarbonylaminomethyl)cyclohexanecarboxaldehyde

In dichloromethane (5 ml), trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylmethanol (0.20 g) was dissolved, followed by the addition of pyridinium chlorochromate (0.23 g). The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby the title compound (0.15 g, 76%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.00 (2H,m), 1.27 (2H,m), 1.40-1.60 (1H,m), 1.44 (9H,s), 1.88 (2H,m), 2.02 (2H,m), 2.18 (1H,m), 3.00 (2H,t,J=6.4Hz), 4.61 (1H,br), 9.62 (1H,s).

MS (FAB) m/z: 242 (M+H)<sup>+</sup>.

[Referential Example 47] 1-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylmethyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (7 ml), trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexane carboxaldehyde (0.13 g) was dissolved, followed by the addition of 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (0.24 g), triethylamine (78 μl) and sodium triacetoxyborohydride (0.17 g). The resulting mixture was stirred at room temperature for 11 hours under an argon gas atmosphere. To the reaction mixture, an aqueous solution of sodium bicarbonate was added, followed by dilution with dichloromethane. The organic layer so separated was dried

over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (0.29 g, 100%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.70-0.90 (4H,m), 1.30-1.50 (2H,m), 1.42 (9H,s), 1.70-1.80 (4H,m), 2.09 (2H,d,  $J=7.3\text{Hz}$ ), 2.46 (4H,m), 2.92 (2H,m), 3.08 (4H,m), 4.53 (1H,br), 7.56 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.78 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.80-8.00 (3H,m), 8.30 (1H,s).

MS (FAB)  $m/z$ : 536[(M+H) $^+$ ,  $\text{Cl}^{35}$ ], 538[(M+H) $^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 48] 1-[trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

A reaction was conducted as in Referential Examples 11 and 12, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.80-1.00 (2H,m), 1.40-1.60 (3H,m), 1.42 (9H,s), 1.60-1.70 (2H,m), 1.70-1.90 (2H,m), 2.30 (1H,m), 2.95 (2H,m), 3.07 (4H,m), 3.58 (2H,br), 3.70 (2H,br), 4.57 (1H,m), 7.58 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.75 (1H,dd,  $J=8.8, 1.5\text{Hz}$ ), 7.90-8.00 (3H,m), 8.30 (1H,s).

MS (FD)  $m/z$ : 549( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 551( $\text{M}^+$ ,  $\text{Cl}^{37}$ ).

[Referential Example 49] N-[trans-4-(N-tert-Butoxycarbonylaminomethyl)cyclohexylcarbonyl]glycine benzyl ester

In the same manner as in Referential Examples 11 and 12, a reaction was conducted using methyl N-tert-butoxycarbonyltranexamate and glycine benzyl ester as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.96(2H,m), 1.44(9H,s), 1.40-1.60(3H,m), 1.80-1.90(2H,m), 1.90-2.00(2H,m), 2.10(1H,m), 2.98(2H,m), 4.08(2H,d,J=4.9Hz), 4.57(1H,br), 5.19(2H,s), 5.97(1H,m), 7.30-7.40(5H,m).

Elementary analysis for  $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_5$

Calculated: C, 65.32; H, 7.97; N, 6.93.

Found: C, 65.05; H, 7.89; N, 7.16.

[Referential Example 50] 1-[N-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylcarbonyl]glycyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (11 ml), N-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylcarbonyl]glycine benzyl ester (0.22 g) was suspended. To the resulting suspension, 10% palladium carbon (water content: about 50%, 50 mg) was added, followed by catalytic hydrogenation at normal pressure and room temperature for 14 hours. After the removal of the catalyst by filtration, the solvent was distilled off under reduced pressure. The residue so obtained was reacted as in Referential Example 12, whereby the title compound (0.32 g, 98%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.80-1.00 (2H,m), 1.30-1.50 (3H,m),  
 1.43 (9H,s), 1.80-2.00 (4H,m), 2.06 (1H,m), 2.95 (2H,m), 3.10-  
 3.20 (4H,m), 3.52 (2H,m), 3.74 (2H,m), 3.94 (2H,d,J=4.4Hz),  
 4.54 (1H,m), 6.40 (1H,m), 7.59 (1H,dd,J=8.8,2.0Hz),  
 7.74 (1H,dd,J=8.8,1.5Hz), 7.80-8.00 (3H,m), 8.30 (1H,s).

MS (FAB) m/z: 607 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 609 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 51] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride

Homopiperazine (5 g) was dissolved in tetrahydrofuran  
 (100 ml) at room temperature. To the resulting solution,  
 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (12.3  
 g) was added in portions, followed by stirring for 3 hours.  
 After completion of the reaction, the solvent was distilled  
 off. The residue was purified by chromatography on a sil-  
 ica gel column (10 to 20% methanol - dichloromethane), fol-  
 lowed by the addition of 1N aqueous hydrochloric acid in  
 ethanol. The solvent was then distilled off. The residue  
 was solidified by the addition of ethanol, whereby powders  
 (7.46 g) were obtained. The resulting powders were reacted  
 as in Referential Example 1, whereby the title compound was  
 obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.00 (2H,br s), 3.10-3.30 (4H,m), 3.30-  
 3.50 (2H,m), 3.55-3.65 (2H,m), 7.72 (1H,d,J=8.8Hz),  
 7.89 (1H,d,J=8.3Hz), 8.17 (1H,d,J=8.8Hz), 8.22-8.28 (2H,m),  
 8.56 (1H,s), 9.29 (2H,br s).

MS (FAB) m/z: 325 (M+H)<sup>+</sup>.

Elementary analysis for C<sub>15</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>2</sub>S·HCl

Calculated: C, 49.89; H, 5.02; N, 7.75; Cl, 19.63.

Found: C, 49.94; H, 5.05; N, 7.47; Cl, 19.65.

5 [Referential Example 52] 1-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexylcarbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine

In the same manner as in Referential Example 48, a reaction was conducted using methyl N-tert-butoxycarbonyltranexamate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]homopiperazine hydrochloride, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.80-1.00 (2H,m), 1.40-1.60 (3H,m), 1.43 (9H,s), 1.60-1.90 (4H,m), 1.90-2.10 (2H,m), 2.30-2.40 (1H,m), 2.97 (2H,m), 3.30-3.50 (4H,m), 3.60-3.80 (4H,m), 4.64 (1H,br), 7.50-7.60 (1H,m), 7.70-7.80 (1H,m), 7.80-8.00 (3H,m), 8.33 and 8.35 (1H, each s).

MS (FAB) m/z: 564 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 566 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Referential Example 53] Methyl 4-(N-tert-butoxycarbonylaminomethyl)benzoate

In the same manner as in Referential Example 44, a reaction was conducted using 4-aminomethylbenzoic acid as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 (9H,s), 3.91 (3H,s), 4.37 (2H,d,J=5.4Hz), 4.92 (1H,br), 7.35 (2H,d,J=8.3Hz),



8.00 (2H, d, J=8.3Hz).

Elementary analysis for  $C_{14}H_{19}NO_4$

Calculated: C, 63.38; H, 7.22; N, 5.28.

Found: C, 63.20; H, 7.02; N, 5.58.

5 [Referential Example 54] 1-[4-(N-tert-butoxycarbonylaminomethyl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 48, a reaction was conducted using methyl 4-(N-tert-butoxycarbonylaminomethyl)benzoate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45 (9H, s), 3.00-3.30 (4H, br), 3.40-4.00 (4H, br), 4.31 (2H, d, J=5.9Hz), 4.90 (1H, br), 7.27 (4H, m), 7.59 (1H, dd, J=8.8, 1.5Hz), 7.75 (1H, d, J=8.8Hz), 7.90-8.00 (3H, m), 8.30 (1H, s).

MS (FAB)  $m/z$ : 544  $[(M+H)^+, \text{Cl}^{35}]$ , 546  $[(M+H)^+, \text{Cl}^{37}]$ .

[Referential Example 55] Methyl 3-(N-tert-butoxycarbonylaminomethyl)benzoate

20 Methyl 3-methylbenzoate (1.00 g) was dissolved in carbon tetrachloride (10 ml), followed by the addition of N-bromosuccinic imide (1.22 g) and 2,2'-azobisisobutyronitrile (catalytic amount). The resulting mixture was heated under reflux for 1 hour under exposure to a mercury lamp. After the insoluble matter was filtered

25

off, the residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 20:1), whereby a colorless oil (1.34 g) was obtained.

5       The colorless oil (0.62 g) so obtained was dissolved in N,N-dimethylformamide (10 ml), followed by the addition of sodium azide (0.38 g). The resulting mixture was stirred at room temperature for 20 hours. After the concentration of the reaction mixture under reduced pressure, 10 the concentrate was diluted with ethyl acetate, washed with water and then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (15 ml). Triphenylphosphine (0.75 g) was added to the resulting solution, followed by stirring at an external temperature of 15 about 50°C for 5 hours. After the addition of about 28% aqueous ammonia (7 ml) and stirring for further 2 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was extracted with ether. Dilute 20 hydrochloric acid was added to the extract to make it acidic. To the water layer so separated, a dilute aqueous solution of sodium hydroxide was added to make it alkaline, followed by extraction with dichloromethane. The extract was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure 25 was dissolved in dichloromethane (7 ml). To the resulting

solution, di-tert-butyl dicarbonate (0.45 g) was added under ice cooling, followed by stirring at room temperature for 3 days. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 5:1), whereby the title compound (0.29 g, 35%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.46(9H,s), 3.91(3H,s), 4.36(2H,d,J=5.9Hz), 4.97(1H,br), 7.40(1H,t,J=7.8Hz), 7.49(1H,d,J=7.8Hz), 7.90-8.00(2H,m).

MS (FAB)  $m/z$ : 266 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 56] Methyl 4-cyanomethylbenzoate

In dichloromethane (20 ml), methyl 4-hydroxymethylbenzoate (1.00 g) was dissolved, followed by the addition of triethylamine (0.9 ml). Under ice cooling, a solution of methanesulfonyl chloride (0.70 g) in dichloromethane (dichloromethane: 5 ml) was added to the resulting solution. The resulting mixture was stirred at room temperature for 15 hours. After dilution with dichloromethane, the reaction mixture was washed with water and was then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in acetonitrile (12 ml). To the resulting solution, potassium cyanide (0.80 g) and 18-Crown-6 (0.16 g) were added, followed by stirring at room temperature for 40 hours. After concentration under reduced pres-

sure, the concentrate was diluted with dichloromethane, washed with water and then, dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane), whereby colorless crystals (0.91 g, 86%) was obtained. A portion of the resulting crystals was recrystallized from a mixed solvent of hexane and ethyl acetate, whereby colorless crystals were obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.82(2H,s), 3.93(3H,s), 7.42(2H,d,J=8.3Hz), 8.06(2H,d,J=8.3Hz).

Elementary analysis for C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub>

Calculated: C, 68.56; H, 5.18; N, 8.00.

Found: C, 68.39; H, 5.29; N, 8.08.

[Referential Example 57] Methyl 4-[2-(tert-butoxycarbonylamino)ethyl]benzoate

Methyl 4-cyanomethylbenzoate (0.20 g) was dissolved in a mixed solvent of methanol (15 ml) and chloroform (0.4 ml). To the resulting solution, platinum dioxide (33 mg) was added, followed by catalytic hydrogenation at room temperature under 3 atmospheric pressure for 3 hours. The catalyst was removed by filtration through Celite and the solvent was distilled off under reduced pressure. The residue was suspended in dichloromethane (5 ml), followed by the addition of triethylamine (160 μl). After the addi-

tion of a solution of di-tert-butyl dicarbonate (0.29 g) in dichloromethane (dichloromethane: 2 ml) under ice cooling, the resulting solution was stirred at room temperature for 13 hours. The reaction mixture was diluted with dichloromethane, washed with water and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 10:1 ~ 5:1), whereby the title compound (0.28 g, 88%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.43(9H,s), 2.86(2H,t,J=6.8Hz), 3.39(2H,m), 3.91(3H,s), 4.53(1H,br), 7.27(2H,d,J=8.3Hz), 7.98(2H,d,J=8.3Hz).

Elementary analysis for  $\text{C}_{15}\text{H}_{21}\text{NO}_4$

Calculated: C, 64.50; H, 7.58; N, 5.01.

Found: C, 64.43; H, 7.35; N, 4.97.

[Referential Example 58] 1-[4-[2-(tert-butoxycarbonylamino)ethyl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 48, the title compound was obtained using methyl 4-[2-(tert-butoxycarbonylamino)ethyl]benzoate and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.42(9H,s), 2.79(2H,t,J=6.8Hz),

3.10 (4H, br), 3.35 (2H, m), 3.40-4.00 (4H, br), 4.50 (1H, br),  
 7.18 (2H, d,  $J=8.3\text{Hz}$ ), 7.24 (2H, d,  $J=8.3\text{Hz}$ ),  
 7.59 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.75 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.90-  
 8.00 (3H, m), 8.30 (1H, s).

5 MS (FAB)  $m/z$ : 558  $[(M+H)^+, Cl^{35}]$ , 560  $[(M+H)^+, Cl^{37}]$ .

[Referential Example 59] Methyl 4-[[ $(3S)$ -1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate

In tetrahydrofuran (50 ml), methyl 4-hydroxybenzoate  
 (1.01 g),  $(3R)$ -1-tert-butoxycarbonyl-3-pyrrolidinol (1.36  
 10 g) and triphenylphosphine (1.73 g) were dissolved, followed  
 by the dropwise addition of a 40% solution (2.87 ml) of di-  
 ethyl azodicarboxylate in toluene under ice cooling. The  
 resulting mixture was stirred at room temperature for 20  
 hours. To the reaction mixture, ethyl acetate and a 10%  
 15 aqueous solution of potassium carbonate were added to sepa-  
 rate the organic layer. The organic layer so separated was  
 washed with a 10% aqueous solution of potassium carbonate  
 and water and dried over anhydrous sodium sulfate. The  
 solvent was then distilled off under reduced pressure. The  
 20 residue was purified by chromatography on a silica gel col-  
 umn (hexane : ethyl acetate = 2:1), whereby the title com-  
 pound (1.60 g, 76%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.46 (9H, s), 2.00-2.20 (2H, m), 3.40-  
 3.70 (4H, m), 3.89 (3H, s), 4.96 (1H, br s), 6.88 (2H, d,  $J=8.8\text{Hz}$ ),  
 25 7.90-8.00 (2H, m).

[Referential Example 60] 4-[[[(3S)-1-tert-Butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid

In the same manner as in Referential Example 11, a reaction was conducted using methyl 4-[[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.45 and 1.47 (9H, each s), 2.10-2.20 (2H, m), 3.40-3.70 (4H, m), 5.00-5.10 (1H, m), 6.98 (2H, d, J=8.8 Hz), 7.97 (2H, d, J=8.8 Hz).

[Referential Example 61] 1-[4-[[[(3S)-1-tert-Butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-[[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.46 (9H, s), 2.00-2.20 (2H, m), 3.00-3.20 (4H, m), 3.40-3.80 (8H, m), 4.88 (1H, br s), 6.82 (2H, d, J=8.3 Hz), 7.20-7.30 (2H, m), 7.60 (1H, dd, J=8.7, 1.9 Hz), 7.76 (1H, dd, J=8.5, 1.7 Hz), 7.90-7.95 (3H, m), 8.30 (1H, s).

Elementary analysis for C<sub>30</sub>H<sub>34</sub>ClN<sub>3</sub>O<sub>6</sub>S

Calculated: C, 60.04; H, 5.71; N, 7.00.

Found: C, 60.05; H, 5.69; N, 6.80.

[Referential Example 62] Methyl 3-[[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate

In the same manner as in Referential Example 59, the title compound was obtained using methyl 3-hydroxybenzoate as a starting material.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)δ: 1.45 and 1.47(9H, each s), 2.05-2.25(2H,m), 3.40-3.70(4H,m), 3.92(3H,s), 4.96(1H,br s), 7.07(1H,d,J=7.8Hz), 7.30-7.40(1H,m), 7.53(1H,d,J=2.0Hz), 7.65(1H,m).

MS (FAB) m/z: 322 (M+H)<sup>+</sup>.

[Referential Example 63] 3-[[[(3S)-1-tert-Butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid

In the same manner as in Referential Example 11, the title compound was obtained using methyl 3-[[[(3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate as a starting material.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.45 and 1.47(9H, each s), 2.05-2.25(2H,m), 3.35-3.65(4H,m), 5.04(1H,br s), 7.05-7.15(1H,m), 7.30-7.40(1H,m), 7.53(1H,s), 7.62(1H,d,J=7.3Hz).

MS (FAB) m/z: 308 (M+H)<sup>+</sup>.

[Referential Example 64]

1-[3-[[[(3S)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine



In the same manner as in Referential Example 12, the title compound was obtained using 3-[[ (3S)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid as a starting material.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45 and 1.46(9H, each s), 2.00-2.20(2H,m), 2.95-3.25(4H,m), 3.40-3.90(8H,m), 4.84(1H,br s), 6.80-6.90(3H,m), 7.20-7.30(1H,m), 7.60(1H,dd,J=8.8,1.5Hz), 7.76(1H,dd,J=8.5,1.7Hz), 7.90-7.95(3H,m), 8.30-8.35(1H,m).

MS (FAB) m/z: 600 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 602 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 65] Methyl 4-[[ (3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate

In the same manner as in Referential Example 59, the title compound was obtained using methyl 4-hydroxybenzoate and (3S)-1-tert-butoxycarbonyl-3-pyrrolidinol as starting materials.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47(9H,s), 2.05-2.25(2H,m), 3.40-3.70(4H,m), 3.89(3H,s), 4.96(1H,br s), 6.88(2H,d,J=8.8Hz), 7.90-8.00(2H,m).

MS (FAB) m/z: 322 (M+H)<sup>+</sup>.

[Referential Example 66] 4-[[ (3R)-1-tert-Butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid

In the same manner as in Referential Example 11, the title compound was obtained using methyl 4-[[ (3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate as a starting

material.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$ : 1.47 and 1.48 (9H, each s), 2.10-2.25 (2H, m), 3.40-3.70 (4H, m), 4.98 (1H, br s), 6.91 (2H, d,  $J=8.8\text{Hz}$ ), 8.00-8.10 (2H, m).

5 MS (FAB)  $m/z$ : 308 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 67] 1-[4-[[ (3R)-1-tert-butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

10 In the same manner as in Referential Example 12, the title compound was obtained using 4-[[ (3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid as a starting material.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.46 (9H, s), 2.00-2.20 (2H, m), 3.00-3.20 (4H, m), 3.40-3.80 (8H, m), 4.89 (1H, br s), 15 6.82 (2H, d,  $J=8.3\text{Hz}$ ), 7.20-7.30 (2H, m), 7.58 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.74 (1H, dd,  $J=8.5, 1.7\text{Hz}$ ), 7.90-7.95 (3H, m), 8.30 (1H, s).

MS (FAB)  $m/z$ : 600 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 602 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

20 [Referential Example 68] Methyl 3-[[ (3R)-1-tert-butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate

In the same manner as in Referential Example 59, the title compound was obtained using methyl 3-hydroxybenzoate and (3S)-1-tert-butoxycarbonyl-3-pyrrolidinol as starting materials.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47 (9H, s), 2.05-2.25 (2H, m), 3.40-

3.70 (4H, m), 3.92 (3H, s), 4.95 (1H, br s), 7.07 (1H, d, J=7.8 Hz),  
7.30-7.40 (1H, m), 7.50-7.55 (1H, m), 7.60-7.70 (1H, m).

MS (FAB) m/z: 322 (M+H)<sup>+</sup>.

[Referential Example 69] 3-[[[(3R)-1-tert-butoxycarbonyl-3-  
5 pyrrolidinyl]oxy]benzoic acid

In the same manner as in Referential Example 11, the  
title compound was obtained using methyl 3-[[[(3R)-1-tert-  
butoxycarbonyl-3-pyrrolidinyl]oxy]benzoate as a starting  
material.

10 <sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ: 1.48 (9H, s), 2.05-2.25 (2H, m), 3.45-  
3.70 (4H, m), 4.97 (1H, br s), 7.10-7.15 (1H, m), 7.35-  
7.45 (1H, m), 7.58 (1H, s), 7.70-7.75 (1H, m).

MS (FAB) m/z: 308 (M+H)<sup>+</sup>.

[Referential Example 70] 1-[3-[[[(3R)-1-tert-  
15 Butoxycarbonylpyrrolidin-3-yl]oxy]benzoyl]-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the  
title compound was obtained using 3-[[[(3R)-1-tert-  
butoxycarbonyl-3-pyrrolidinyl]oxy]benzoic acid as a start-  
20 ing material.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45 and 1.46 (9H, each s), 2.00-  
2.20 (2H, m), 2.95-3.25 (4H, m), 3.40-3.90 (8H, m), 4.84 (1H, br  
s), 6.80-6.90 (3H, m), 7.20-7.30 (1H, m),  
7.60 (1H, dd, J=8.5, 1.7 Hz), 7.76 (1H, dd, J=8.5, 2.0 Hz), 7.90-  
25 7.95 (3H, m), 8.30-8.35 (1H, m).

MS (FAB) m/z: 600 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 602 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 71] 4-(2-Amino-5-pyrimidyl)benzoic acid

In the same manner as in Referential Example 2, the  
5 title compound was obtained using 2-amino-5-bromopyrimidine  
as a starting material.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.81(2H,d,J=8.8Hz), 8.00(2H,d,J=8.8Hz),  
8.84(2H,s).

MS (FAB) m/z: 216 (M+H)<sup>+</sup>.

10 [Referential Example 72] 1-tert-Butoxycarbonyl-4-  
[(methoxycarbonyl)methylene]piperidine

In tetrahydrofuran (40 ml), methyl dimethylphosphono-  
acetate (1.8 ml) was dissolved. To the resulting solution,  
60% oily sodium hydride (450 mg) was added under ice cool-  
15 ing, followed by stirring under the same condition. After  
the addition of a solution of 1-(tert-butoxycarbonyl)-4-  
piperidone (2.0 g) in tetrahydrofuran (tetrahydrofuran: 10  
ml) and stirring at room temperature for 30 minutes, the  
reaction mixture was diluted with ethyl acetate. To the  
20 diluted solution, 2N hydrochloric acid was added. The or-  
ganic layer was separated, washed with a saturated aqueous  
solution of sodium bicarbonate and saturated aqueous NaCl  
solution, and dried over anhydrous sodium sulfate. The  
solvent was then distilled off under reduced pressure. The  
25 residue was purified by chromatography on a silica gel col-

umn (hexane : ethyl acetate = 6:1), whereby the title compound (2.35 g, 92%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47(9H,s), 2.28(2H,t,J=5.9Hz),  
2.94(2H,t,J=5.9Hz), 3.48(2H,t,J=5.9Hz), 3.50(2H,t,J=5.9Hz),  
5 3.70(3H,s), 5.72(1H,s).

Elementary analysis for  $\text{C}_{13}\text{H}_{21}\text{NO}_4$

Calculated: C, 61.16; H, 8.29; N, 5.49.

Found: C, 61.14; H, 8.34; N, 5.20.

[Referential Example 73] Methyl (1-tert-  
10 butoxycarbonylpiperidin-4-yl)acetate

In ethanol (10 ml), 1-tert-butoxycarbonyl-4-  
[(methoxycarbonyl)methylene]piperidine (875 mg) was dissolved, followed by the addition of 10% palladium carbon  
(water content: about 50%, 730 mg). The resulting mixture  
15 was subjected to catalytic hydrogenation under normal pressure at room temperature for 3 days. After the removal of the catalyst by filtration, the solvent was distilled off under reduced pressure, whereby the title compound (871 mg, 99%) was obtained.

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.16(2H,m), 1.45(9H,s), 1.65(2H,m),  
1.93(1H,m), 2.25(2H,d,J=6.8Hz), 2.72(2H,br), 3.68(3H,s),  
4.08(2H,br).

MS (FAB)  $m/z$ : 258 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 74] (1-tert-Butoxycarbonylpiperidin-  
25 4-yl)acetic acid

In the same manner as in Referential Example 11, the title compound was obtained using methyl (1-tert-butoxycarbonylpiperidin-4-yl)acetate as a starting material.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.18(2H,m), 1.45(9H,s), 1.73(2H,m), 1.94(1H,m), 2.29(2H,d,J=6.8Hz), 2.72(2H,m), 4.10(2H,br). MS (EI) m/z: 243 M<sup>+</sup>.

[Referential Example 75] 1-[(1-tert-butoxycarbonylpiperidin-4-yl)acetyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using (1-tert-butoxycarbonylpiperidin-4-yl)acetic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.05(2H,m), 1.43(9H,s), 1.63(2H,m), 1.91(1H,m), 2.14(2H,d,J=6.8Hz), 2.66(2H,m), 3.07(4H,br s), 3.56(2H,br s), 3.67(2H,br s), 4.02(2H,br), 7.58(1H,dd,J=8.8,2.0Hz), 7.75(1H,d,J=8.8Hz), 7.91(1H,d,J=8.8Hz), 7.93(1H,d,J=8.8Hz), 7.92(1H,s), 8.30(1H,s).

MS (FAB) m/z: 536 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 538 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 76] 3-(1-tert-butoxycarbonylpiperidin-4-yl)propionic acid

A reaction was conducted using ethyl 1-tert-

butoxycarbonylisonipecotinate and diisobutylaluminum hydride, whereby the corresponding aldehyde derivative was obtained. The resulting derivative was treated as in Referential Examples 72, 73 and 74, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.10 (2H, m), 1.41 (1H, m), 1.45 (9H, s), 1.60 (2H, q,  $J=7.8\text{Hz}$ ), 1.66 (2H, m), 2.39 (2H, t,  $J=7.8\text{Hz}$ ), 2.67 (2H, m), 4.09 (2H, br).

MS (FAB)  $m/z$ : 258 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 77] 1-[3-(1-tert-butoxycarbonylpiperidin-4-yl)propionyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 3-(1-tert-butoxycarbonylpiperidin-4-yl)propionic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.04 (2H, m), 1.35 (1H, m), 1.44 (9H, s), 1.47 (2H, q,  $J=7.8\text{Hz}$ ), 1.57 (2H, m), 2.24 (2H, t,  $J=7.8\text{Hz}$ ), 2.61 (2H, m), 3.07 (4H, br s), 3.56 (2H, br s), 3.71 (2H, br s), 4.04 (2H, br), 7.58 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.75 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.90 (1H, d,  $J=8.8\text{Hz}$ ), 7.91 (1H, s), 7.92 (1H, d,  $J=8.8\text{Hz}$ ), 8.30 (1H, s).

MS (FAB)  $m/z$ : 550 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 552 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 78] (E)-3-(4-Pyridyl)acrylic acid

In the same manner as in Referential Examples 72 and 74, the title compound was obtained using isonicotinic aldehyde as a starting material.

5  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 6.79(1H,d,J=16.6Hz),  
7.56(1H,d,J=16.6Hz), 7.66(2H,d,J=5.9Hz),  
8.62(2H,d,J=5.9Hz), 12.72(1H,br s).  
MS (EI)  $m/z$ : 149 $\text{M}^+$ .

[Referential Example 79] 1-Methoxycarbonyl-3-pyrroline

10 In dichloromethane (20 ml), 3-pyrroline (1.1 ml) was dissolved, followed by the addition of triethylamine (2.6 ml) and methyl chloroformate (1.2 ml) under ice cooling. The resulting mixture was stirred at room temperature for 17 hours. The residue obtained by distilling the reaction  
15 mixture under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (0.95 g, 52%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.73(3H,s), 4.00-4.20(4H,m), 5.70-  
5.90(2H,m).

20 [Referential Example 80] Methyl 4-trifluoromethanesulfonyloxybenzoate

In dichloromethane (20 ml), methyl 4-hydroxybenzoate (1.99 g) was dissolved, followed by the addition of pyridine (2.4 ml) and trifluoromethanesulfonic anhydride (3.0  
25 ml) under ice cooling. After stirring at room temperature



for 6 hours, the reaction mixture was added with pyridine (1.5 ml) and trifluoromethanesulfonic anhydride (1.0 ml) again. The resulting mixture was stirred for 5 hours. Dichloromethane and an aqueous solution of sodium bicarbonate were added to the reaction mixture. The organic layer so separated was washed with a 10% aqueous citric acid solution and saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (5% ethyl acetate - hexane), whereby the title compound (3.22 g, 86%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.95(3H,s), 7.36(2H,d,J=8.8Hz), 8.15(2H,d,J=8.8Hz).

MS (FAB)  $m/z$ : 285 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 81] Methyl 4-(1-methoxycarbonylpyrrolidin-3-yl)benzoate

In N,N-dimethylformamide (25 ml), methyl 4-trifluoromethanesulfonyloxybenzoate (1.05 g), 1-methoxycarbonyl-3-pyrroline (1.0 g), lithium chloride (0.51 g), palladium (II) acetate (53 mg) and tri(2-furyl)phosphine (100 mg) were dissolved, followed by the addition of diisopropylethylamine (2.8 ml). Under an argon gas atmosphere, the resulting mixture was stirred at 90°C for 11 hours and then, at 100°C for 7 hours. The residue obtained by dis-

tilling off the solvent under reduced pressure was added with dichloromethane and water. The organic layer so separated was washed with water and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 9:1 ~ 5:1).

The purified product was dissolved in methanol (30 ml), followed by the addition of 10% palladium carbon (water content: about 50%, 186 mg) and ammonium formate (197 mg).

The resulting mixture was heated under reflux for 2 hours. After the removal of the catalyst by filtration, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (10% ethyl acetate - toluene), whereby the title compound (241 mg, 25%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.95-2.10 (1H,m), 2.25-2.35 (1H,m), 3.30-3.35 (4H,m), 3.55-3.75 (1H,m), 3.72 and 3.73 (3H, each s), 3.80-3.90 (1H,m), 3.91 (3H,s), 7.30 (2H,d,J=3.8Hz), 8.00 (2H,d,J=8.3Hz).

MS (FAB)  $m/z$ : 264 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 82] 4-(1-tert-Butoxycarbonylpyrrolidin-3-yl)benzoic acid

In methanol (10 ml), methyl 4-(1-methoxycarbonylpyrrolidin-3-yl)benzoate (0.24 g) was dissolved. The resulting solution was added with 8N hydro-

chloric acid (30 ml), followed by heating under reflux for 40 hours. The residue obtained by distilling off the solvent under reduced pressure was dissolved in N,N-dimethylformamide (30 ml). To the resulting solution, 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (0.30 g) and then diisopropylethylamine (0.40 ml) were added, followed by stirring at room temperature for 15 hours. The residue obtained by distilling off the solvent under reduced pressure was distributed in ethyl acetate and a 10% aqueous citric acid solution. The organic layer so separated was washed with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 10% methanol - dichloromethane), whereby the title compound (234 mg) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48 (9H,m), 1.90-2.00 (1H,m), 2.20-2.30 (1H,m), 3.20-3.90 (5H,m), 7.20-7.30 (2H,m), 8.00-8.10 (2H,m).

MS (EI) m/z: 291M<sup>+</sup>.

[Referential Example 83] 1-[4-(3RS)-1-tert-Butoxycarbonylpyrrolidin-3-yl]benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-(1-tert-

butoxycarbonylpyrrolidin-3-yl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 and 1.60 (9H, each s), 1.80-2.00 (1H, m), 2.10-2.20 (1H, m), 3.00-4.00 (13H, m), 7.10-7.30 (4H, m), 7.55-7.65 (1H, m), 7.70-7.80 (1H, m), 7.85-8.00 (3H, m), 8.30 (1H, s).

[Referential Example 84] (3S)-3-Amino-1-tert-butoxycarbonylpyrrolidine

In the same manner as in Referential Example 55, the title compound was obtained using (3R)-1-tert-butoxycarbonyl-3-methanesulfonyloxypyrrolidine (1.50 g) as a starting material.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.46 (9H, s), 1.98-2.11 (2H, m), 2.95-3.10 (1H, m), 3.26-3.60 (4H, m).

MS (FAB) m/z: 187 (M+H)<sup>+</sup>.

[Referential Example 85] (3S)-3-[(6-Chloronaphthalen-2-yl)sulfonamide]pyrrolidine trifluoroacetate

In the same manner as in Referential Example 1, a reaction was conducted using (3S)-3-amino-1-tert-butoxycarbonylpyrrolidine as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.69-1.80 (1H, m), 1.88-1.99 (1H, m), 2.95-3.28 (4H, m), 3.75-3.84 (1H, m), 7.71 (1H, m), 7.91 (1H, m), 8.10-

8.30(4H,m), 8.53(1H,s), 8.91(1H,br s), 9.06(1H,br s).

[Referential Example 86] (3S)-3-Amino-1-[(6-chloronaphthalen-2-yl)sulfonyl]pyrrolidine

In trifluoroacetic acid, (3R)-1-tert-butoxycarbonyl-3-methanesulfonyloxypyrrolidine was dissolved. After the resulting solution was concentrated under reduced pressure, diethyl ether was added to the concentrate, followed by the removal of the supernatant. The residue was reacted as in Referential Example 1, whereby the corresponding sulfonamide derivative was obtained as a crude product. The crude product was subjected to azide formation and reduction as in Referential Example 55, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.38-1.53(3H,m), 1.72-1.83(1H,m), 2.81-2.89(1H,m), 3.20-3.39(4H,m), 7.69(1H,dd,J=8.8,1.9Hz), 7.87(1H,d,J=8.8Hz), 8.12(1H,d,J=8.8Hz), 8.21(1H,s), 8.26(1H,d,J=8.8Hz), 8.39(1H,s).

MS (FAB) m/z: 311 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 313 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 87] 4-Benzylamino-1-tert-butoxycarbonylpiperidine

In dichloromethane (500 ml), 1-tert-butoxycarbonyl-4-piperidone (7.00 g) was dissolved, followed by the addition of benzylamine (4.03 ml) and sodium triacetoxyborohydride (11.91 g). The resulting mixture was stirred overnight at room temperature. After the reaction mixture was

concentrated under reduced pressure, the residue was dissolved in ethyl acetate. The resulting mixture was washed with water and saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 1:1), whereby the title compound (7.46 g, 76%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.24-1.37 (2H,m), 1.45 (9H,s), 1.80-1.90 (2H,m), 2.62-2.70 (1H,m), 2.75-2.85 (1H,m), 2.98-3.07 (1H,m), 3.78-3.90 (3H,m), 3.95-4.10 (1H,m), 7.21-7.34 (5H,m).

MS (FD)  $m/z$ : 290 $\text{M}^+$ .

[Referential Example 88] 4-Amino-1-tert-butoxycarbonylpiperidine acetate

In methanol (2 ml) and acetic acid (30 ml), 4-benzylamino-1-tert-butoxycarbonylpiperidine (4.04 g) was dissolved, followed by the addition of 10% palladium carbon (water content: about 50%, 3.06 g). The resulting mixture was subjected to catalytic hydrogenation overnight under medium pressure (3 atmospheric pressure). After the removal of the catalyst by filtration, the filtrate was distilled off under reduced pressure. The residue was solidified in ethyl acetate, whereby the title compound (2.23 g, 57%) was obtained.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.10-1.23 (2H, m), 1.39 (9H, s), 1.69-1.77 (2H, m), 1.80 (3H, s), 2.50 (2H, s), 2.67-2.88 (2H, m), 3.80-3.90 (1H, m).

MS (FAB)  $m/z$ : 201 ( $M+H$ ) $^+$ .

5 Elementary analysis for  $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_2 \cdot \text{CH}_3\text{CO}_2\text{H}$

Calculated: C, 53.16; H, 9.37; N, 10.33.

Found: C, 53.51; H, 9.10; N, 9.93.

[Referential Example 89] 4-[(6-Chloronaphthalen-2-yl)sulfonamido]piperidine trifluoroacetate

10 In the same manner as in Referential Example 1, the title compound was obtained using 4-amino-1-tert-butoxycarbonylpiperidine acetate and 6-chloro-2-naphthylsulfonyl chloride as starting materials.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 1.47-1.60 (2H, m), 1.68-1.78 (2H, m), 2.81-15 2.95 (2H, m), 3.10-3.20 (2H, m), 3.29-3.40 (1H, m), 7.70 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.91 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.11-8.15 (2H, m), 8.21 (1H, s), 8.31 (1H, br s), 8.50 (1H, s), 8.55 (1H, br s).

MS (FAB)  $m/z$ : 325 [ $(M+H)^+$ ,  $\text{Cl}^{35}$ ], 327 [ $(M+H)^+$ ,  $\text{Cl}^{37}$ ].

20 [Referential Example 90] Ethyl (1RS)-4-trifluoromethanesulfonyloxy-3-cyclohexenecarboxylate

Diisopropylamine (0.99 ml) was dissolved in tetrahydrofuran (50 ml), followed by the dropwise addition of *n*-butyl lithium (a 1.59M hexane solution, 3.70 ml) at  $-78^\circ\text{C}$ .

25 After the dropwise addition of ethyl 4-

oxocyclohexanecarboxylate (1.00 g) dissolved in tetrahydrofuran (5 ml) to the reaction mixture and stirring for 15 minutes, N-phenyltrifluoromethanesulfonimide (2.10 g) dissolved in tetrahydrofuran (5 ml) was added dropwise to the reaction mixture. The reaction mixture was heated to 0°C, stirred for one hour and then concentrated under reduced pressure. The residue was purified by chromatography on a neutral alumina column (hexane : ethyl acetate = 9:1), whereby the title compound (838 mg, 47%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.27(3H,t,J=7.3Hz), 1.88-1.99(1H,m), 2.10-2.18(1H,m), 2.38-2.50(4H,m), 2.55-2.64(1H,m), 4.16(2H,q,J=7.3Hz), 5.77(1H,br s).

MS (FAB) m/z: 303 (M+H)<sup>+</sup>.

[Referential Example 91] Ethyl (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylate

In the same manner as in Referential Example 7, a reaction was conducted using ethyl (1RS)-4-trifluoromethanesulfonyloxy-3-cyclohexenecarboxylate as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.28(3H,t,J=7.3Hz), 1.80-1.91(1H,m), 2.19-2.25(1H,m), 2.40-2.57(4H,m), 2.59-2.67(1H,m), 4.17(2H,q,J=7.3Hz), 6.36(1H,br s), 7.26(2H,dd,J=4.9,1.5Hz), 8.53(2H,dd,J=4.9,1.5Hz).

MS (FAB) m/z: 232 (M+H)<sup>+</sup>.

[Referential Example 92] (1RS)-4-(4-Pyridyl)-3-



cyclohexenecarboxylic acid

In the same manner as in Referential Example 8, a reaction was conducted using ethyl (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylate as a starting material, the title  
5 compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.70-1.82 (1H,m), 2.10-2.19 (1H,m), 2.42-2.65 (5H,m), 6.99 (1H,br s), 8.02 (2H,d,J=6.8Hz), 8.80 (2H,d,J=6.8Hz).

MS (FAB)  $m/z$ : 204 ( $\text{M}+\text{H}$ ) $^+$ .

10 [Referential Example 93] cis-, trans-4-(4-Pyridyl)cyclohexanecarboxylic acid

In the same manner as in Referential Example 73, the title compound was obtained using (1RS)-4-(4-pyridyl)-3-cyclohexenecarboxylic acid as a starting material.

15 MS (FAB)  $m/z$ : 206 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 94] 4-(1-tert-Butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid

In 1,2-dimethoxyethane (30 ml), 4-(1-tert-butoxycarbonyl-4-trifluoromethanesulfonyloxy-1,2,3,6-tetrahydropyridine (Synthesis, 993, 1991) (3.59 g) was dissolved, followed by the addition of 4-carboxyphenylboric acid (3.60 g), lithium chloride (1.38 g), tetrakis(triphenylphosphine) palladium (0.62 g) and an aqueous solution of sodium carbonate (2M, 16.3 ml). The resulting mixture was  
20 heated under reflux for 2 hours under an argon gas atmos-  
25

phere. To the reaction mixture, 1N hydrochloric acid was added. The resulting mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1). The purified product was pulverized and washed in a mixed solvent of hexane and ethyl acetate (hexane : ethyl acetate = 5:1), whereby the title compound (462 mg, 14%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.50(9H,s), 2.56(2H,br s), 3.66(2H,m), 4.12(2H,br s), 6.19(1H,br s), 7.47(2H,d,J=8.3Hz), 8.07(2H,d,J=8.3Hz).

MS (FAB)  $m/z$ : 304 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 95] 4-(1-tert-butoxycarbonylpiperidin-4-yl)benzoic acid

In the same manner as in Referential Example 73, the title compound was obtained by using 4-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)benzoic acid as a starting material.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48(9H,s), 1.60-1.71(2H,m), 1.80-1.89(2H,m), 2.69-2.90(3H,m), 4.20-4.35(2H,m), 7.31(2H,d,J=8.3Hz), 8.05(2H,d,J=8.3Hz).

MS (FAB)  $m/z$ : 306 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 96] 1-[4-(1-tert-butoxycarbonyl-

1,2,3,6-tetrahydropyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-(1-tert-butoxycarbonyl-  
 5 1,2,3,6-tetrahydropyridin-4-yl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.49(9H,s), 2.48(2H,br s), 3.10(4H,br),  
 10 3.62(2H,t,J=5.9Hz), 3.70(4H,br), 4.08(2H,br s), 6.05(1H,br s), 7.25(2H,d,J=8.3Hz), 7.34(2H,d,J=8.3Hz), 7.59(1H,dd,J=8.8,2.0Hz), 7.75(1H,dd,J=8.8,2.0Hz), 7.90-7.96(3H,m), 8.30(1H,s).

MS (FAB) m/z: 596 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 598 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

15 [Referential Example 97] 1-[4-(1-tert-butoxycarbonylpiperidin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a reaction was conducted using 4-(1-tert-  
 20 butoxycarbonylpiperidin-4-yl)benzoic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47(9H,s), 1.49-1.63(2H,m), 1.72-  
 25 1.80(2H,m), 2.59-2.68(1H,m), 2.71-2.86(2H,m), 2.92-

3.30 (4H, m), 3.45-4.95 (4H, m), 4.16-4.31 (2H, m),  
 7.18 (2H, d, J=8.3 Hz), 7.24 (2H, d, J=8.3 Hz),  
 7.59 (1H, dd, J=8.8, 2.0 Hz), 7.75 (1H, dd, J=8.8, 2.0 Hz), 7.90-  
 7.94 (3H, m), 8.30 (1H, s).

5 MS (FAB) m/z: 598 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 600 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 98] (3RS)-3-Amino-1-tert-  
 butoxycarbonylpyrrolidine

In methanol (30 ml), 3-aminopyrrolidine (0.54 g) was  
 dissolved under ice cooling, followed by the addition of  
 10 diisopropylethylamine (720  $\mu$ l) and 2-(tert-  
 butoxycarbonyloxyimino)-2-phenylacetonitrile (0.84 g). The  
 resulting mixture was gradually heated to room temperature  
 and stirred for 11 hours. The residue obtained by distill-  
 ing off the solvent under reduced pressure was purified by  
 15 chromatography on a silica gel column (dichloromethane ~ 5%  
 methanol - dichloromethane), whereby the title compound  
 (0.59 g, 94%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.45 (9H, s), 2.0-2.3 (2H, m), 3.1-4.0 (5H, m).

[Referential Example 99] (3RS)-1-tert-Butoxycarbonyl-3-  
 20 [(6-chloronaphthalen-2-yl)sulfonamide]pyrrolidine

In the same manner as in Referential Example 1, the  
 title compound was obtained using (3RS)-3-amino-1-tert-  
 butoxycarbonylpyrrolidine as a starting material.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.37 (9H, s), 1.60-2.10 (2H, m), 3.00-  
 25 3.50 (4H, m), 3.88 (1H, br), 4.96 (1H, br), 7.50-7.60 (1H, m),

7.80-7.90 (4H,m), 8.43 (1H,s).

MS (FAB) m/z: 411 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 413 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 100] (3RS)-1-tert-Butoxycarbonyl-3-[4-(4-pyridyl)benzamide]pyrrolidine

5 In the same manner as in Referential Example 12, the title compound was obtained using (3RS)-3-amino-1-tert-butoxycarbonylpyrrolidine and 4-(4-pyridyl)benzoic acid as starting materials.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48 (9H,s), 1.90-2.10 (1H,m), 2.20-  
10 2.30 (1H,m), 3.30-3.40 (1H,m), 3.40-3.60 (2H,m), 3.70-  
3.80 (1H,m), 4.65-4.75 (1H,m), 6.25-6.35 (1H,m),  
7.52 (2H,d,J=5.9Hz), 7.71 (2H,d,J=8.3Hz), 7.88 (2H,d,J=8.3Hz),  
8.70 (2H,d,J=5.4Hz).

MS (FAB) m/z: 368 (M+H)<sup>+</sup>.

15 [Referential Example 101] 6-Chloro-N-methoxy-N-methylnicotinamide

Under ice cooling, 6-chloronicotinic acid (5.00 g) was suspended in dichloromethane (150 ml), followed by the addition of a catalytic amount of N,N-dimethylformamide and  
20 oxalyl chloride (5.30 ml). The resulting mixture was stirred at room temperature for 23 hours. The residue obtained by concentrating the reaction mixture was dissolved in dichloromethane (100 ml), followed by the addition of N,O-dimethylhydroxylamine hydrochloride (6.18 g) and tri-  
25 ethylamine (13.3 ml) under ice cooling. After stirring at

room temperature for 6 hours, the reaction mixture was diluted with dichloromethane (150 ml), washed with a saturated aqueous solution of sodium bicarbonate, water and saturated aqueous NaCl solution and then dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (6.08 g, 96%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.39(3H,s), 3.56(3H,s), 7.39(1H,d,J=8.3Hz), 8.03(1H,dd,J=8.3,2.4Hz), 8.78(1H,d,J=2.4Hz).

[Referential Example 102] 6-Chloronicotinaldehyde

In tetrahydrofuran (8 ml), 6-chloro-N-methoxy-N-methylnicotinamide (500 mg) was dissolved, followed by the dropwise addition of diisobutylaluminum hydride (a 0.95M hexane solution, 2.88 ml) at  $-78^\circ\text{C}$  in an argon gas atmosphere. The resulting mixture was stirred for 3 hours and then, at room temperature, for 2 hours. After the reaction mixture was cooled to  $-20^\circ\text{C}$ , saturated aqueous NaCl solution (2 ml) was added thereto, followed by stirring for 30 minutes. The insoluble matter was filtered off. The residue was washed with ethyl acetate. The filtrate and the washing were combined together. The mixture was washed with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The solvent was then distilled off

under reduced pressure, whereby the title compound (346 mg, 98%) was obtained as a crude product. The product was provided for the subsequent reaction without purification.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.52 (1H, d,  $J=8.3\text{Hz}$ ),

5 8.14 (1H, dd,  $J=8.3, 2.2\text{Hz}$ ), 8.87 (1H, d,  $J=2.2\text{Hz}$ ), 10.10 (1H, s).

[Referential Example 103] 1-tert-Butoxycarbonyl-4-methanesulfonylpiperazine

In dichloromethane (40 ml), N-tert-butoxycarbonylpiperazine (2.00 g) was dissolved, followed  
10 by the addition of triethylamine (1.78 ml). To the resulting solution, methanesulfonyl chloride (0.91 ml) was added dropwise under ice cooling. After stirring for one hour under ice cooling, the reaction mixture was diluted with dichloromethane (20 ml), washed with a 5% aqueous citric  
15 acid solution, water and saturated aqueous NaCl solution and dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was recrystallized from a mixed solvent of ethyl acetate and hexane, whereby the title compound (2.58 g, 91%)  
20 was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47 (9H, s), 2.79 (3H, s),

3.19 (4H, t,  $J=5.1\text{Hz}$ ), 3.55 (4H, t,  $J=5.1\text{Hz}$ ).

[Referential Example 104] 1-tert-Butoxycarbonyl-4-[[ (2RS)-2-(6-chloropyridin-3-yl)-2-hydroxyethyl]sulfonyl]piperazine

25 In tetrahydrofuran (8 ml), 1-tert-butoxycarbonyl-4-

methanesulfonylpiperazine (838 mg) was dissolved, followed by the addition of tert-butyl lithium (a 1.7M pentane solution, 1.72 ml) at -78°C in an argon gas atmosphere. The resulting mixture was stirred for 2 hours. After the dropwise addition of a solution of 6-chloronicotinaldehyde (346 mg) in tetrahydrofuran (tetrahydrofuran: 4 ml) and stirring at -78°C for 3 hours, the reaction mixture was added with isopropanol (1 ml). The resulting mixture was heated to room temperature and diluted with ethyl acetate. The diluted solution was washed with water and saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was recrystallized from ethyl acetate, whereby the title compound (532 mg, 54%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.46(9H,s), 3.11(1H,dd,J=14.1,2.2Hz), 3.21(1H,dd,J=14.1,9.8Hz), 3.23-3.33(4H,m), 3.52-3.57(4H,m), 3.70(1H,br s), 5.37(1H,br), 7.36(1H,d,J=8.3Hz), 7.72(1H,dd,J=8.3,2.4Hz), 8.41(1H,d,J=2.4Hz).

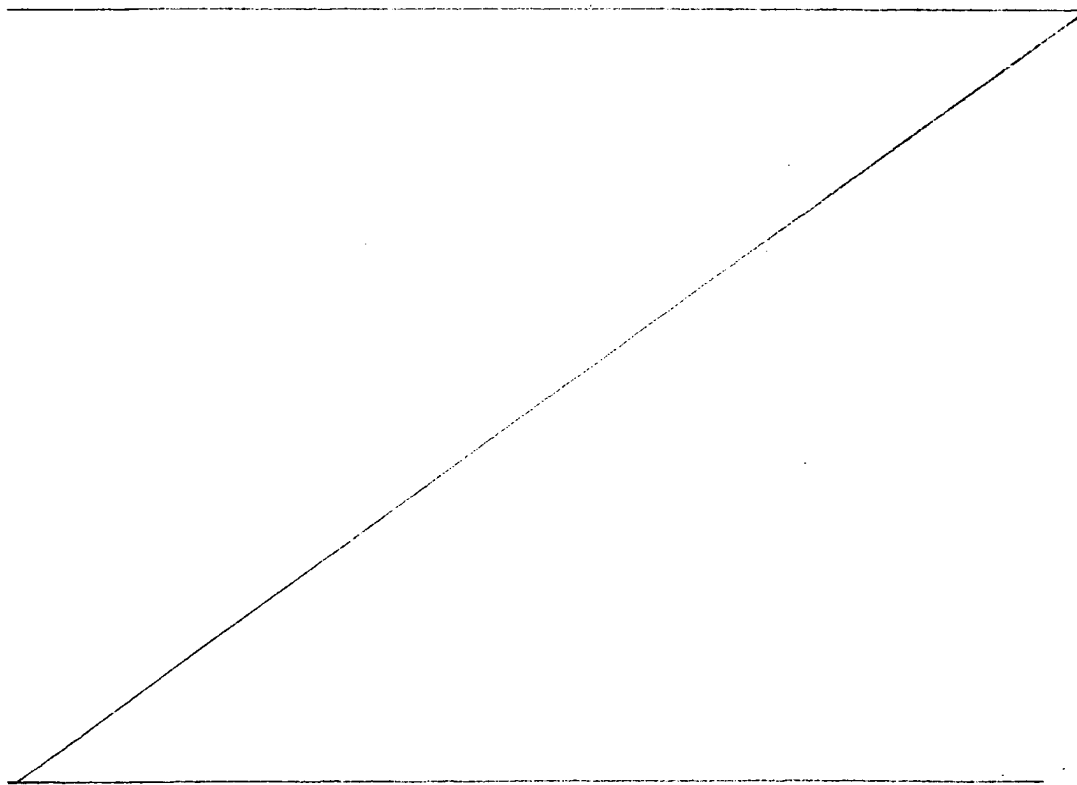
MS (FAB) m/z: 405 (M+H)<sup>+</sup>.

[Referential Example 105] 1-tert-Butoxycarbonyl-4-[(E)-2-(6-chloropyridin-3-yl)ethylene]sulfonylpiperazine

In dichloromethane (10 ml), 1-tert-butoxycarbonyl-4-[[ (2RS)-2-(6-chloropyridin-3-yl)-2-hydroxyethyl]-sulfonylpiperazine (465 mg) was dissolved, followed by the addition of N-methylmorpholine (0.152 ml) and N,N-dimethyl-



4-aminopyridine (14.1 mg). Under an argon atmosphere, p-toluenesulfonyl chloride (263 mg) was added under ice cooling. After stirring at room temperature for 2 hours, N,N-dimethyl-4-aminopyridine (141 mg) was added further and the  
5 resulting mixture was stirred at room temperature for 3 hours. After dilution with dichloromethane (20 ml), the reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate, water and saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate.  
10 The residue obtained by distilling off the solvent under reduced pressure



was purified by chromatography on a silica gel column (dichloromethane : methanol = 100:1), whereby the title compound (414 mg, 93%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45(9H,s), 3.19(4H,br), 3.55(4H,br),  
 5 6.73(1H,d,J=15.6Hz), 7.40(1H,d,J=8.3Hz),  
 7.43(1H,d,J=15.6Hz), 7.76(1H,dd,J=8.3,2.5Hz),  
 8.50(1H,d,J=2.5Hz).

Elementary analysis for C<sub>16</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>3</sub>S

Calculated: C, 49.54; H, 5.72; N, 10.83; Cl, 9.14; S, 8.27.

10 Found: C, 49.54; H, 5.73; N, 10.63; Cl, 9.44; S, 8.15.

[Referential Example 106] 1-(4-Bromo-2-methylbenzoyl)-4-  
 [(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a  
 reaction was conducted using 4-bromo-2-methylbenzoic acid  
 15 and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine  
 hydrochloride as starting materials, whereby the title  
 compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.13(3H,s), 2.80-4.10(8H,m),  
 6.89(1H,d,J=8.3Hz), 7.30(1H,dd,J=8.3,2.0Hz),  
 20 7.35(1H,d,J=2.0Hz), 7.60(1H,dd,J=8.8,2.0Hz),  
 7.74(1H,dd,J=8.8,2.0Hz), 7.90-7.95(3H,m), 8.30(1H,br s).

MS (FAB) m/z: 507 [(M+H)<sup>+</sup>, Br<sup>79</sup>], 509 [(M+H)<sup>+</sup>, Br<sup>81</sup>].

[Referential Example 107] 3-Methyl-4-(4-pyridyl)benzoic  
 acid hydrochloride

25 In the same manner as in Referential Example 6, a

reaction was conducted using 4-bromo-3-methylbenzoic acid as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.36(3H,s), 7.50(1H,d,J=7.8Hz),  
5 7.92(1H,d,J=7.8Hz), 7.97(1H,s), 8.08(2H,d,J=6.4Hz),  
8.99(2H,d,J=6.4Hz).

MS (FAB) m/z: 214 (M+H)<sup>+</sup>.

[Referential Example 108] 4-(2-Methyl-4-pyridyl)benzoic acid hydrochloride

10 In the same manner as in Referential Example 2, a reaction was conducted using 4-bromo-2-methylpyridine as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.81(3H,s), 8.10-8.16(4H,m),  
8.23(1H,dd,J=6.4,1.5Hz), 8.36(1H,d,J=1.5Hz),  
15 8.85(1H,d,J=6.4Hz).

MS (FAB) m/z: 214 (M+H)<sup>+</sup>.

[Referential Example 109] 1,4-Dibenzyl-2-methoxycarbonylmethylpiperazine

In toluene (250 ml), N,N'-dibenzylethylenediamine (12  
20 ml) and triethylamine (12 ml) were dissolved, followed by the dropwise addition of methyl 3-bromocrotonate (7.0 ml) under ice cooling. The resulting mixture was stirred at room temperature for 24 hours. After the addition of triethylamine (2.0 ml), the resulting mixture was stirred  
25 at room temperature for 71 hours. The insoluble matter was

filtered off and the filtrate was distilled under reduced pressure. The residue was added with 10% hydrochloric acid (300 ml) and crystals so precipitated were removed by filtration. Ethyl acetate was added to the filtrate.

5 Potassium carbonate was added to the water layer so separated to make it alkaline. Ethyl acetate was added to the resulting mixture. The organic layer so separated was washed with saturated aqueous NaCl solution and dried over anhydrous potassium carbonate. The solvent was then

10 distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (10.7 g, 62%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.30-2.70 (8H,m), 3.11 (1H,br s), 3.40-

15 3.80 (4H,m), 3.60 (3H,s), 7.20-7.40 (10H,m).

MS (FAB)  $m/z$ : 339 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 110] 1-[(6-Chloronaphthalen-2-yl)sulfonyl]-3-methoxycarbonylmethylpiperazine

In acetic acid (40 ml), 1,4-dibenzyl-2-  
20 methoxycarbonylmethylpiperazine (2.04 g) was dissolved, followed by the addition of 10% palladium carbon (water content: about 50%, 2.00 g). The resulting mixture was subjected to catalytic reduction at room temperature for 4 hours under 4 atmospheric pressure. After removal of the  
25 catalyst by filtration, the residue obtained by distilling the filtrate under reduced pressure was added with

dichloromethane and a saturated aqueous solution of potassium bicarbonate. The insoluble matter so precipitated was filtered off. The organic layer so separated was washed with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was dissolved in dichloromethane (30 ml), followed by the addition of 6-chloro-2-naphthylsulfonyl chloride (782 mg). The resulting mixture was stirred at 0°C for 2 hours. To the reaction mixture, triethylamine (410 µl) was added, followed by stirring at 0°C for further three hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (dichloromethane ~ 3% methanol - dichloromethane), whereby the title compound (759 mg, 33%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.71(1H, br s), 2.15-2.55(4H, m), 2.90-3.05(2H, m), 3.15-3.25(1H, m), 3.60-3.70(5H, m), 7.55-7.60(1H, m), 7.75-7.80(1H, m), 7.85-7.95(3H, m), 8.30(1H, s).

MS (FAB) m/z: 383 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 385 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 111] 4-tert-Butoxycarbonyl-1-[(3-chloro-1-propyl)sulfonyl]piperazine

Under an argon gas atmosphere, 1-tert-butoxycarbonylpiperazine (3.00 g) and triethylamine (2.24 ml) were dissolved in dichloromethane (40 ml) under ice cooling, followed by the addition of 3-chloro-1-

propanesulfonic acid chloride (1.96 g). The resulting mixture was stirred for 20 minutes under ice cooling and then, at room temperature for 10 minutes. The reaction mixture was diluted with dichloromethane, washed with water and saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was recrystallized from a mixed solvent of ethyl acetate and hexane, whereby the title compound (4.36 g, 83%) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41(9H,s), 2.27-2.33(2H,m), 3.08(2H,t,J=7.3Hz), 3.26(4H,t,J=4.9Hz), 3.53(4H,t,J=4.9Hz), 3.69(2H,t,J=6.1Hz).

MS (FAB) m/z: 327 (M+H)<sup>+</sup>

Elementary analysis for C<sub>12</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>4</sub>S

Calculated: C, 44.10; H, 7.09, Cl, 10.85; N, 8.57; S, 9.81.

Found: C, 44.18; H, 7.11; Cl, 10.69; N, 8.23; S, 9.76.

[Referential Example 112] 4-tert-Butoxycarbonyl-1-[(3-hydroxy-1-propyl)sulfonyl]piperazine

In N,N-dimethylformamide (10 ml), 4-tert-butoxycarbonyl-1-[(3-chloro-1-propyl)sulfonyl]piperazine (1.18 g) was dissolved, followed by the addition of potassium acetate (1.06 g). After stirring at room temperature for 2 hours, the reaction mixture was stirred under heat at 100°C for 3 hours. The reaction mixture was diluted with ethyl acetate, followed by the addition of water and a saturated aqueous solution of sodium

bicarbonate. After stirring, the organic layer so separated was washed with a 5% aqueous citric acid solution, water and saturated aqueous NaCl solution. After drying over anhydrous sodium sulfate, the residue  
5 obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (20 ml). To the resulting solution, water and lithium hydroxide monohydrate (221 mg) were added, followed by stirring at room temperature for 18 hours. Ethyl acetate and saturated  
10 aqueous NaCl solution were added to the reaction mixture to separate an organic layer. From the water layer, another organic layer was extracted with ethyl acetate. The organic layers were combined together, washed with saturated aqueous NaCl solution and dried over anhydrous  
15 sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was recrystallized from a mixed solvent of ethyl acetate and hexane, whereby the title compound (944 mg, 84%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47(9H,s), 2.04-2.11(2H,m),  
20 3.06(2H,t,J=7.6Hz), 3.25(4H,t,J=4.9Hz), 3.53(4H,t,J=4.9Hz), 3.80(2H,q,J=5.4Hz).

MS (FAB)  $m/z$ : 309 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$

Calculated: C, 46.74; H, 7.84; N, 9.08; S, 10.40.

25 Found: C, 46.80; H, 7.92; N, 9.05; S, 10.59.

[Referential Example 113] 4-tert-Butoxycarbonyl-1-[(3-

methoxymethyloxy-1-propyl)sulfonyl]piperazine

In dichloromethane (60 ml), 4-tert-butoxycarbonyl-1-[(3-hydroxy-1-propyl)sulfonyl]piperazine (3.00 g) was dissolved. To the resulting solution,

5 diisopropylethylamine (2.72 ml) was added, followed by the addition of methoxymethyl chloride (1.11 ml) under ice cooling. After stirring at room temperature for 15 hours, the reaction mixture was diluted with dichloromethane, washed with water, 5% aqueous citric acid solution and  
10 saturated aqueous NaCl solution and then dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby the title compound (3.32 g, 97%)  
15 was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 (9H, s), 2.06-2.13 (2H, m), 3.03 (2H, m), 3.25 (4H, t, J=4.9Hz), 3.36 (3H, s), 3.52 (4H, t, J=4.9Hz), 3.63 (2H, t, J=5.4Hz), 4.61 (2H, s).

MS (FAB) m/z: 353 (M+H)<sup>+</sup>.

20 Elementary analysis for C<sub>14</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub>S

Calculated: C, 47.71; H, 8.01; N, 7.95; S, 9.10.

Found: C, 47.77; H, 8.18; N, 7.97; S, 9.16.

[Referential Example 114] 4-tert-Butoxycarbonyl-1-[(E)-4-chloro-β-[2-(methoxymethyloxy)ethyl]-β-

25 styrylsulfonyl]piperazine and 4-tert-butoxycarbonyl-1-[(Z)-



4-chloro- $\beta$ -[2-(methoxymethyloxy)ethyl]- $\beta$ -styrylsulfonyl]piperazine

Under an argon gas atmosphere, 4-tert-butoxycarbonyl-1-[(3-methoxymethyloxy-1-propyl)sulfonyl]piperazine (800  
5 mg) was dissolved in tetrahydrofuran (10 ml), followed by the dropwise addition of tert-butyl lithium (a 1.7M hexane solution, 1.47 ml) at  $-78^{\circ}\text{C}$ . The resulting mixture was stirred at  $-78^{\circ}\text{C}$  for one hour. After the addition of trimethylsilyl chloride (0.317 ml) and stirring at  $-78^{\circ}\text{C}$   
10 for 90 minutes, tert-butyl lithium (a 1.7M hexane solution, 1.47 ml) was added dropwise to the reaction mixture and stirring was effected at  $-78^{\circ}\text{C}$  for 90 minutes. At  $-78^{\circ}\text{C}$ , a solution of p-chlorobenzaldehyde (352 mg) in tetrahydrofuran (tetrahydrofuran: 8 ml) was added dropwise  
15 to the reaction mixture. After stirring for 2 hours, the temperature of the reaction mixture was allowed to rise back to room temperature over 15 hours, at which temperature it was stirred for 6 hours. Under ice cooling, a 5% citric acid solution (20 ml) and ethyl acetate (150  
20 ml) were added to the reaction mixture. The organic layer so separated was washed with water and saturated aqueous NaCl solution and then dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by  
25 chromatography on a silica gel column (hexane : ethyl acetate = 3:1 ~ 2:1), whereby the title compound was

obtained as an E-form (307 mg, 28%) and Z-form (751 mg, 70%).

E-form:

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.42 (9H, s), 2.87 (2H, t, J=7.3Hz), 3.21-  
5 3.28 (4H, m), 3.35 (3H, s), 3.46-3.56 (4H, m),  
3.80 (2H, t, J=7.3Hz), 4.60 (2H, s), 7.40 (2H, d, J=8.5Hz),  
7.46 (2H, d, J=8.5Hz), 7.54 (1H, s).

Z-form:

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.43 (9H, s), 2.77 (2H, dt, J=6.4, 1.0Hz),  
10 2.91-2.98 (4H, m), 3.19-3.25 (4H, m), 3.38 (3H, s),  
3.82 (2H, t, J=6.4Hz), 4.66 (2H, s), 7.07 (1H, s),  
7.32 (2H, d, J=8.6Hz), 7.35 (2H, d, J=8.6Hz).

[Referential Example 115] 6-Chloro-1-phenylsulfonylindole

At -78°C, n-butyl lithium (a 1.61M hexane solution,  
15 3.34 ml) was added to a solution of 6-chloroindole (777 mg)  
in tetrahydrofuran (25 ml), followed by heating to -40°C  
over 1 hour. The reaction mixture was cooled back to -78°C  
and added with benzenesulfonyl chloride (867 μl). The  
resulting mixture was heated to room temperature over 3  
20 hours. Water was added to the reaction mixture, followed  
by extraction with dichloromethane. The organic layers  
were combined, dried over anhydrous sodium sulfate and  
concentrated under reduced pressure. The residue was  
25 purified by chromatography on a silica gel column (40 g of  
silica gel, hexane : ethyl acetate = 5:7). The white solid  
so obtained was recrystallized from ethanol, whereby the

title compound (826 mg, 55%) was obtained as a white solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 6.64 (1H, d,  $J=3.9\text{Hz}$ ),  
7.21 (1H, dd,  $J=8.3, 1.2\text{Hz}$ ), 7.42–7.60 (5H, m),  
7.88 (2H, d,  $J=7.3\text{Hz}$ ), 8.03 (1H, s).

5 Elementary analysis for  $\text{C}_{14}\text{H}_{10}\text{ClNO}_2\text{S}$

Calculated: C, 57.63; H, 3.45; Cl, 12.15; N, 4.80;  
S, 10.99.

Found: C, 57.48; H, 3.75; Cl, 12.34; N, 4.87;  
S, 10.87.

10 In the same manner as in Referential Example 115, the  
compounds which will be described below in Referential  
Examples 116 and 117 were synthesized.

[Referential Example 116] 5-Chloro-1-phenylsulfonylindole

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 6.61 (1H, d,  $J=3.9\text{Hz}$ ),  
15 7.26 (1H, dd,  $J=8.3, 2.0\text{Hz}$ ), 7.45 (2H, t,  $J=7.3\text{Hz}$ ),  
7.50 (1H, d,  $J=2.0\text{Hz}$ ), 7.56 (1H, m), 7.59 (1H, d,  $J=3.9\text{Hz}$ ),  
7.86 (2H, m), 7.92 (1H, d,  $J=8.3\text{Hz}$ ).

Elementary analysis for  $\text{C}_{14}\text{H}_{10}\text{ClNO}_2\text{S}$

Calculated: C, 57.63; H, 3.45; Cl, 12.15; N, 4.80;  
20 S, 10.99.

Found: C, 57.82; H, 3.58; Cl, 11.91; N, 4.79;  
S, 10.92.

[Referential Example 117] 5-Bromo-1-phenylsulfonylindole

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 6.60 (1H, d,  $J=3.7\text{Hz}$ ),  
25 7.42 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.45 (2H, t,  $J=8.8\text{Hz}$ ),

7.55(1H,d,J=8.8Hz), 7.57(1H,d,J=3.7Hz), 7.73(1H,d,J=2.0Hz),  
7.86(2H,d,J=8.8Hz), 7.87(1H,d,J=1H,d,J=8.8Hz).

Elementary analysis for  $C_{14}H_{10}BrNO_2S$

Calculated: C, 50.01; H, 3.00; N, 4.17; Br, 23.77; S, 9.54.

5 Found: C, 49.96; H, 2.97; N, 4.02; Br, 23.90; S, 9.53.

[Referential Example 118] 1-Phenylsulfonyl-5-trimethylsilylethynylindole

In tetrahydrofuran (7.00 ml), 5-bromo-1-phenylsulfonylindole (1.50 g) and triphenylphosphine (351  
10 mg) were dissolved. Triethylamine (20 ml), N,N-dimethylformamide (7.00 ml), trimethylsilylacetylene (945  
μl) and palladium acetate (100 mg) were added to the resulting solution at room temperature, followed by heating  
under reflux for 5 hours. After the reaction mixture was  
15 allowed to cool down to room temperature, ethyl acetate and water were added to the reaction mixture to separate the  
organic layer. The resulting organic layer was dried over anhydrous sodium sulfate and then distilled under reduced  
pressure to remove the solvent. The residue was purified  
20 by chromatography on a silica gel column (hexane : ethyl acetate = 20:1 to 10:1), whereby the title compound (935  
mg, 59%) was obtained as a white solid.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 0.24(9H,s), 6.62(1H,d,J=3.9Hz),  
7.42(1H,dd,J=8.8,1.5Hz), 7.44(2H,t,J=7.8Hz),  
25 7.52(1H,d,J=7.8Hz), 7.56(1H,d,J=3.9Hz), 7.66(1H,d,J=1.5Hz),  
7.85(2H,d,J=7.8Hz), 7.92(1H,d,J=8.8Hz).

MS (FAB) m/z: 354 (M+H)<sup>+</sup>

[Referential Example 119] 5-Chloro-1-ethylindole

In benzene (10 ml), 5-chloroindole (1.52 g) was dissolved, followed by the addition of a 50% aqueous solution of sodium hydroxide (10 ml), tetrabutylammonium bromide (161 mg) and bromoethane (1.64 g). The resulting mixture was stirred at room temperature for 40 hours. After the addition of a saturated aqueous solution of ammonium chloride to the reaction mixture, water and dichloromethane were added to separate the organic layer. After the organic layer was dried over anhydrous sodium sulfate, the residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:20), whereby the title compound (1.68 g, 93%) was obtained as colorless crystals.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.46(3H,t,J=7.3Hz), 4.16(2H,q,J=7.3Hz), 6.43(1H,d,J=2.4Hz), 7.14(1H,d,J=2.4Hz), 7.15(1H,d,J=8.3Hz), 7.26(1H,J=8.3Hz), 7.59(1H,s).

MS (EI) m/z: 179 (M<sup>+</sup>, Cl<sup>35</sup>), 181 (M<sup>+</sup>, Cl<sup>37</sup>).

[Referential Example 120] 6-Chloro-1-phenylsulfonylindole-2-sulfonyl chloride

After the dropwise addition of tert-butyl lithium (a 1.56M pentane solution, 1.78 ml) to a solution of 6-chloro-1-phenylsulfonylindole (777 mg) in ether (12 ml) at -78°C, the mixture was heated to 0°C over 30 minutes. The reaction

mixture was stirred for 1 hour and then cooled back to -78°C. Sulfurdioxide was then introduced into the reaction mixture. After heating to room temperature over 1 hour, stirring was conducted for 1 hour. The reaction mixture was concentrated under reduced pressure. Hexane was added to the concentrate, followed by concentration under reduced pressure again. The residue was dissolved in dichloromethane. To the resulting solution, N-chlorosuccinimide (390 mg) was added at 0°C, followed by heating over 1 hour to room temperature. Stirring was then conducted for 30 minutes. Dichloromethane and water were added to the reaction mixture to separate the organic layer. The resulting organic layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was recrystallized from methanol, whereby the title compound (857 mg, 79%) was obtained as a white solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.39(1H,dd,J=8.3,1.6Hz), 7.48-7.67(4H,m), 7.68(1H,s), 8.08(2H,d,J=7.3Hz), 8.35(1H,s).

Elementary analysis for  $\text{C}_{14}\text{H}_9\text{ClNO}_4\text{S}_2$

Calculated: C, 43.09; H, 2.32; Cl, 18.17; N, 3.59; S, 16.43.

Found: C, 43.32; H, 2.67; Cl, 18.25; N, 3.64; S, 16.22.

In the same manner as in Referential Example 120, compounds which will be described below in Referential

Examples 121 to 128 were synthesized.

[Referential Example 121] 1-Phenylsulfonylindole-2-sulfonyl chloride

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.40 (1H, t,  $J=7.6\text{Hz}$ ), 7.45–7.53 (2H, m),  
 5 7.57–7.67 (2H, m), 7.69 (1H, d,  $J=7.8\text{Hz}$ ), 7.73 (1H, s),  
 8.08 (2H, d,  $J=7.3\text{Hz}$ ), 8.31 (1H, d,  $J=8.8\text{Hz}$ ).

MS (EI)  $m/z$ : 355 $\text{M}^+$ .

Elementary analysis for  $\text{C}_{14}\text{H}_{10}\text{ClNO}_4\text{S}_2$

Calculated: C, 47.26; H, 2.83; Cl, 9.96; N, 3.94; S, 18.02.

10 Found: C, 47.33; H, 3.08; Cl, 10.04; N, 3.98; S,  
 18.18.

[Referential Example 122] 5-Chloro-1-phenylsulfonylindole-2-sulfonyl chloride

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.46–7.54 (2H, m), 7.58 (1H, dd,  $J=9.3, 2.0\text{Hz}$ ),  
 15 7.63 (1H, t,  $J=7.3\text{Hz}$ ), 7.64 (1H, s), 7.67 (1H, d,  $J=2.0\text{Hz}$ ),  
 8.06 (2H, d,  $J=7.3\text{Hz}$ ), 8.26 (1H, d,  $J=9.3\text{Hz}$ ).

MS (EI)  $m/z$ : 291 ( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 293 ( $\text{M}^+$ ,  $\text{Cl}^{37}$ ).

Elementary analysis for  $\text{C}_{14}\text{H}_9\text{Cl}_2\text{NO}_4\text{S}_2$

20 Calculated: C, 43.09; H, 2.32; Cl, 18.27; N, 3.59; S,  
 16.43.

Found: C, 42.98; H, 2.51; Cl, 18.36; N, 3.59 S, 16.47.

[Referential Example 123] 5-Chloro-1-ethylindole-2-sulfonyl chloride

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.52 (3H, t,  $J=7.3\text{Hz}$ ), 4.59 (2H, q,  $J=7.3\text{Hz}$ ),  
 25 7.36 (1H, s), 7.39 (1H, d,  $J=8.8\text{Hz}$ ), 7.45 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),

7.73(1H,d,J=2.0Hz).

MS (EI) m/z: 277 [ $M^+$ ,  $Cl^{35}$ ], 279 [ $M^+$ ,  $Cl^{37}$ ]

[Referential Example 124] 1-Phenylsulfonyl-5-trimethylsilylethynylindole-2-sulfonyl chloride

5  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 0.26(9H,s), 7.48(2H,t,J=7.8Hz),  
6.61(1H,t,J=7.8Hz), 7.65(1H,s), 7.69(1H,dd,J=8.8,1.5Hz),  
7.79(1H,d,J=1.5Hz), 8.04(2H,d,J=7.8Hz), 8.24(1H,d,J=8.8Hz).

MS (FAB) m/z: 452 [ $(M+H)^+$ ,  $Cl^{35}$ ], 454 [ $(M+H)^+$ ,  $Cl^{37}$ ]

10 [Referential Example 125] 5-Chlorobenzo[b]furan-2-sulfonyl  
chloride

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 7.57(1H,dd,J=8.8,2.0Hz), 7.59(1H,s),  
7.61(1H,d,J=8.8Hz), 7.76(1H,d,J=2.0Hz).

MS (EI) m/z: 250 ( $M^+$ ,  $Cl^{35}$ ), 252 ( $M^+$ ,  $Cl^{37}$ ).

Elementary analysis for  $C_8H_4Cl_2O_3S$

15 Calculated: C, 38.27; H, 1.61; Cl, 28.24; S, 12.77.

Found: C, 38.33; H, 1.71; Cl, 28.16; S, 12.57.

[Referential Example 126] 6-Chlorobenzo[b]furan-2-sulfonyl  
chloride

20  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 7.43(1H,dd,J=8.8,2.0Hz), 7.62(1H,s),  
7.69(1H,s), 7.70(1H,d,J=8.8Hz).

MS (EI) m/z: 250 ( $M^+$ ,  $Cl^{35}$ ), 252 ( $M^+$ ,  $Cl^{37}$ ).

Elementary analysis for  $C_8H_4Cl_2O_3S$

Calculated: C, 38.27; H, 1.61; Cl, 28.24; S, 12.77.

Found: C, 38.31; H, 1.60; Cl, 28.34; S, 12.60.

25 [Referential Example 127] 5-Chlorobenzo[b]thiophene-2-



sulfonyl chloride

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.57(1H, dd,  $J=8.8, 2.0\text{Hz}$ ),

7.85(1H, d,  $J=8.8\text{Hz}$ ), 7.96(1H, d,  $J=2.0\text{Hz}$ ), 8.08(1H, s).

MS (FD)  $m/z$ : 266 ( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 268 ( $\text{M}^+$ ,  $\text{Cl}^{37}$ ).

5 [Referential Example 128] 6-Chlorobenzo[b]thiophene-2-sulfonyl chloride

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.51(1H, dd,  $J=8.3, 1.5\text{Hz}$ ),

7.90(1H, d,  $J=8.3\text{Hz}$ ), 7.92(1H, s), 8.11(1H, s).

MS (FAB)  $m/z$ : 266 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 268 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

10 [Referential Example 129] 1-tert-Butoxycarbonyl-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]piperazine

To a solution of 5-chloro-1-phenylsulfonylindole-2-sulfonyl chloride (4.41 g) in dichloromethane (75 ml), tert-butyl-1-piperazine carboxylate (2.21 g) and

15 triethylamine (1.65 ml) were added under ice cooling. The resulting mixture was stirred at room temperature for 3 hours. After completion of the reaction, water and

dichloromethane were added to the reaction mixture. The organic layer so separated was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (ethyl acetate : n-hexane = 1:20), whereby the title compound (3.63 g, 60%) was obtained as colorless crystals.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45(9H, s), 3.35-3.42(4H, br), 3.50-

3.55(4H,br), 7.40-7.48(4H,m), 7.53-7.58(2H,m), 8.00-8.05(2H,m), 8.23(1H,d,J=8.8Hz).

In the same manner as in Referential Example 129, compounds which will be described below in Referential Examples 130 to 133 were synthesized.

[Referential Example 130] 1-tert-Butoxycarbonyl-4-[(1-phenylsulfonylindol-2-yl)sulfonyl]piperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45(9H,s), 3.34-3.44(4H,br), 3.48-3.56(4H,br), 7.33(1H,t,J=7.3Hz), 7.36-7.45(2H,m), 7.47-7.61(4H,m), 8.04(2H,d,J=7.3Hz), 8.29(1H,d,J=8.8Hz).

MS (EI) m/z: 505M<sup>+</sup>.

[Referential Example 131] 1-tert-Butoxycarbonyl-4-[(5-chloro-1-ethylindol-2-yl)sulfonyl]piperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41(3H,t,J=7.3Hz), 1.43(9H,s), 3.16-3.23(4H,m), 3.48-3.55(4H,m), 4.45(2H,q,J=7.3Hz), 7.03(1H,s), 7.32-7.34(2H,m), 7.66(1H,d,J=2.0Hz).

MS (EI) m/z: 427 (M<sup>+</sup>, Cl<sup>35</sup>), 429 (M<sup>+</sup>, Cl<sup>37</sup>).

[Referential Example 132] 1-tert-Butoxycarbonyl-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]homopiperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47(9H,s), 1.98-2.17(2H,m), 3.42-3.57(8H,m), 7.28(1H,s), 7.41-7.46(3H,m), 7.53-7.57(2H,m), 8.05(2H,d,J=7.3Hz), 8.20(1H,d,J=9.3Hz).

MS (FAB) m/z: 554 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 556 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 133] cis-1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3,5-dimethylpiperazine

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.07 (6H, d,  $J=6.4\text{Hz}$ ), 2.45-2.55 (2H, m),  
 2.95-3.05 (2H, m), 3.75-3.80 (2H, m), 7.35-7.50 (4H, m), 7.50-  
 7.60 (2H, m), 8.00-8.05 (2H, m), 8.22 (1H, d,  $J=9.3\text{Hz}$ ).  
 MS (FAB)  $m/z$ : 468  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 470  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

5 [Referential Example 134] 1-[(5-Chloro-1-  
 phenylsulfonylindol-2-yl)sulfonyl]-3-  
 (ethoxycarbonyl)piperazine

A saturated solution of hydrochloride in ethanol was  
 added to tert-butyl 1-(3-  
 10 ethoxycarbonyl)piperazinecarboxylate (3.97 g) and the  
 mixture was stirred for 30 minutes. After the solvent was  
 distilled off under reduced pressure, the residue was  
 suspended in dichloromethane (200 ml). To the resulting  
 suspension, 5-chloro-1-phenylsulfonylindole-2-sulfonyl  
 15 chloride (6.00 g) and triethylamine (6.40 ml) were added,  
 followed by stirring at room temperature for 3 hours.  
 Water and dichloromethane were added to the reaction  
 mixture. The organic layer so separated was dried over  
 anhydrous sodium sulfate and distilled under reduced  
 20 pressure to remove the solvent. The residue was purified  
 by chromatography on a silica gel column (methanol :  
 dichloromethane = 1:20), whereby the title compound (4.44  
 g, 56%) was obtained as colorless crystals.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.24 (3H, t,  $J=6.8\text{Hz}$ ), 2.87-2.95 (1H, m),  
 25 3.11-3.28 (3H, m), 3.57-3.66 (2H, m), 3.91-3.98 (1H, m),  
 4.17 (2H, q,  $J=6.8\text{Hz}$ ), 7.38-7.48 (4H, m), 7.55-7.59 (2H, m),

8.03(2H,d,J=7.8Hz), 8.21(1H,d,J=9.3Hz).

MS (EI) m/z: 511 ( $M^+$ ,  $Cl^{35}$ ), 513 ( $M^+$ ,  $Cl^{37}$ )+.

[Referential Example 135] 1-tert-Butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

5        To 1-tert-butoxycarbonyl-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]piperazine (4.84 g), a 0.5N methanol solution of sodium hydroxide (20 ml) was added, followed by stirring at room temperature for 1 hour. Under ice cooling, a saturated aqueous solution of ammonium  
10       chloride was added to the reaction mixture. Water and dichloromethane were then added to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by  
15       chromatography on a silica gel column (methanol : dichloromethane = 1:20), whereby the title compound (3.33 g, 93%) was obtained as colorless powder.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.40(9H,s), 3.05-3.14(4H,m), 3.48-3.57(4H,m), 6.96(1H,d,J=2.0Hz), 7.33(1H,dd,J=8.8,2.0Hz),  
20       7.38(1H,d,J=8.8Hz), 7.67(1H,d,J=2.0Hz), 8.78(1H,br).  
MS (FAB) m/z: 400 [ $(M+H)^+$ ,  $Cl^{35}$ ], 402 [ $(M+H)^+$ ,  $Cl^{37}$ ].

In the same manner as in Referential Example 135, the compound shown in Referential Example 136 was synthesized.

[Referential Example 136] 1-[(5-Chloroindol-2-yl)sulfonyl]-3-methoxycarbonylpiperazine  
25

In the same manner as in Referential Example 135, the

title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.70-2.82 (1H,m), 2.84-2.97 (2H,m), 3.06-3.16 (1H,m), 3.37-3.46 (1H,m), 3.61 (1H,dd,J=8.3,3.4Hz), 3.69-3.80 (1H,m), 3.75 (3H,s), 6.98 (1H,s),  
5 7.32 (1H,dd,J=8.8,2.0Hz), 7.38 (1H,d,J=8.8Hz), 7.67 (1H,s),  
8.80 (1H,s).

MS (EI) m/z: 357 ( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 359 ( $\text{M}^+$ ,  $\text{Cl}^{37}$ ) $^+$ .

[Referential Example 137] 3-(N-Methylcarbamoyl)-1-[(5-chloroindol-2-yl)sulfonyl]piperazine

10 In tetrahydrofuran (25 ml), 1-[(5-chloroindol-2-yl)sulfonyl]-3-methoxycarbonylpiperazine (480 mg) was dissolved. After a 0.2N methanol solution (7 ml) of sodium hydroxide and water (2 ml) were added to the resulting solution and the mixture was stirred at room temperature  
15 for 1 hour, the solvent was distilled off under reduced pressure. The resulting yellow amorphous substance (520 mg) was dissolved in N,N-dimethylformamide (60 ml). At room temperature, 1-hydroxybenzotriazole (18.1 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (334  
20 mg), methylamine hydrochloride (90.5 mg) and N-methylmorpholine (271 mg) were added to the resulting solution, followed by stirring at room temperature for 12 hours. The solvent was then distilled off under reduced pressure. Water and ethyl acetate were added to the  
25 residue to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate and distilled under

reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol: dichloromethane = 1:50), whereby the title compound (140 mg, 29%) was obtained as a brown amorphous solid.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.39-2.52 (2H,m), 2.64 (3H,d,J=3.9Hz), 2.18-2.30 (1H,m), 2.94-3.00 (1H,m), 3.20-3.37 (2H,m), 3.57-3.66 (1H,m), 6.90-6.95 (1H,br), 7.22-7.27 (1H,br), 7.44-7.49 (1H,m), 7.66-7.78 (2H,m), 8.04-8.17 (3H,m), 12.24 (1H,m).

[Referential Example 138] 1-[(5-Chloroindol-2-yl)sulfonyl]piperazine hydrochloride

In methanol (100 ml), 1-tert-butoxycarbonyl-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]piperazine (3.63 g) was dissolved. Under ice cooling, a 0.2N methanol solution of sodium hydroxide (100 ml) was added to the resulting solution, followed by stirring at room temperature for 12 hours. After a saturated aqueous solution of ammonium chloride was added to the reaction mixture under ice cooling, water and dichloromethane were added to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure. After the solid so precipitated was collected by filtration, it was dissolved in saturated ethanol hydrochloride, followed by stirring for 30 minutes. The reaction mixture was distilled under reduced pressure to remove the solvent, followed by drying

under reduced pressure, whereby the title compound (1.25 g, 54%) was obtained as colorless powder.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.25-3.43(8H,br), 7.46(1H,d,J=8.8Hz), 7.64(1H,d,J=8.8Hz), 7.93(1H,s), 9.33(1H,br), 12.70(1H,br).

5 MS (EI)  $m/z$ : 298 ( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 300 ( $\text{M}^+$ ,  $\text{Cl}^{37}$ ).

Elementary analysis for  $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{O}_2\text{S}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$

Calculated: C, 41.75; H, 4.67; Cl, 20.54; N, 12.17;

S, 9.29.

Found: C, 41.78; H, 4.98; Cl, 20.40; N, 11.88;

10 S, 9.34.

[Referential Example 139] 1-tert-Butoxycarbonyl-4-[(5-chloro-1-methylindol-2-yl)sulfonyl]piperazine

Sodium hydride (about 60% in oil, 50.3 mg) washed twice with petroleum ether was suspended in tetrahydrofuran  
15 (10 ml), followed by the addition of a solution of 1-tert-butoxycarbonyl-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (457 mg) in tetrahydrofuran (10 ml) under ice cooling. The resulting mixture was stirred for 30 minutes. Under ice cooling, iodomethane (179 mg) was added to the reaction  
20 mixture. The resulting mixture was heated to room temperature and stirred for 85 hours. Water and diethyl ether were added to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent.  
25 The residue was purified by chromatography on a silica gel column (methanol: dichloromethane = 1:50), whereby the

title compound (270 mg, 57%) was obtained as colorless powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.42(9H,s), 3.14-3.21(4H,m), 3.48-3.55(4H,m), 3.96(3H,s), 7.06(1H,s), 7.31(1H,d,J=9.3Hz), 7.36(1H,d,J=9.3,2.0Hz), 7.66(1H,d,J=2.0Hz).

MS (FAB) m/z: 413 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 415 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 140] 1-tert-Butoxycarbonyl-4-[(5-chloro-1-ethoxycarbonylmethylindol-2-yl)sulfonyl]piperazine

In the same manner as in Example 139, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.27(3H,t,J=7.3Hz), 1.43(9H,s), 3.10-3.19(4H,m), 3.45-3.53(4H,m), 4.22(2H,q,J=7.3Hz), 5.15(2H,s), 7.15(1H,s), 7.17(1H,d,J=8.8Hz), 7.26(1H,s), 7.36(1H,dd,J=8.8,2.0Hz), 7.68(1H,d,J=2.0Hz).

MS (FAB) m/z: 485 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 487 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 141] cis-1-[(4-Bromobenzoyl)-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-2,6-dimethylpiperazine

In dichloromethane (40 ml), cis-1-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3,5-dimethylpiperazine (1.30 g) was dissolved. To the resulting suspension, diisopropylethylamine (645 μl) was added under ice cooling, followed by the dropwise addition of a solution of 4-bromobenzoyl chloride (0.74 g) in dichloromethane (5 ml).

Stirring was then effected at room temperature for 3 hours.



A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture. The organic layer thus separated was washed with 0.5N hydrochloric acid and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1 to 1:1), whereby the title compound (1.8 g, 97%) was obtained as a pale yellow amorphous.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45(6H,d,J=6.8Hz), 3.05-3.15(2H,m), 3.74(2H,m), 4.40(2H,br), 7.23(2H,d,J=8.8Hz), 7.40-7.50(4H,m), 7.50-7.60(4H,m), 8.00-8.05(2H,m), 8.24(1H,d,J=9.3Hz).

MS (EI) m/z: 649 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 651 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 142] Ethyl-2-(4-pyridyl)-5-pyrimidinecarboxylic acid

Sodium ethoxide (590 mg) was dissolved in anhydrous ethanol (50 ml) at room temperature. To the resulting solution, 4-amidinopyridine hydrochloride (1.31 g) was added, followed by the dropwise addition of a solution of ethyl 2,2-diformylacetate (1.20 g) in anhydrous ethanol (50 ml). The resulting mixture was heated under reflux for 6 hours. To the residue obtained by distilling off the solvent under reduced pressure, dichloromethane and water were added. The organic layer thus separated was dried over anhydrous sodium sulfate. After the solvent was

concentrated under reduced pressure, the residue was crystallized in ethanol, whereby the title compound (279 mg, 15%) was obtained as colorless crystals.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.46(3H,t,J=7.3Hz), 4.48(2H,q,J=7.3Hz),  
5 8.35(2H,d,J=5.9Hz), 8.82(2H,d,J=5.9Hz), 9.38(2H,s).

MS (FAB)  $m/z$ : 230 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_2$

Calculated: C, 62.87; H, 4.84; N, 18.33.

Found: C, 62.80; H, 4.78; N, 18.25.

10 [Referential Example 143] 2-(4-Pyridyl)-5-pyrimidinecarboxylic acid

In the same manner as in Referential Example 11, a reaction was effected using the ethyl 2-(4-pyridyl)-5-pyrimidinecarboxylate instead as a starting material,  
15 whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 8.32(2H,d,J=5.9Hz), 8.82(2H,d,J=5.9Hz),  
9.38(2H,s).

MS (FAB)  $m/z$ : 201 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_2 \cdot 0.1\text{H}_2\text{O}$

20 Calculated: C, 59.17; H, 3.58; N, 20.70.

Found: C, 59.09; H, 3.49; N, 20.69.

[Referential Example 144] 1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, a  
25 reaction was effected using 5-bromo-2-pyrimidinecarboxylic

acid and 1-[(5-chloroindol-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.14-3.17 (2H,m), 3.25-3.29 (2H,m), 3.52-3.55 (2H,m), 3.92-3.95 (2H,m), 7.97 (1H,s), 7.32-7.40 (2H,m), 7.69 (1H,s), 8.79 (1H,br,s), 8.84 (2H,s).

MS (FAB)  $m/z$ : 484 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$  and  $\text{Br}^{79}$ ], 486 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$  and  $\text{Br}^{81}$ ,  $\text{Cl}^{37}$  and  $\text{Br}^{79}$ ], 488 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$  and  $\text{Br}^{81}$ ].

[Referential Example 145] 6-Chloro-2-mercaptobenzothiazole

Under ice cooling, a solution of p-chloroaniline (5.70 g) in acetic acid (7 ml) was added dropwise to disulfur dichloride (25.0 ml) over 30 minutes, followed by stirring at room temperature for 3 hours and then at about 80°C for 3 hours. Benzene (50 ml) was added to the reaction mixture. The green crystals were collected by filtration and washed with benzene. The resulting crystals were dissolved in ice water (500 ml) and the solution was stirred for 1 hour. To the reaction mixture, a 6N aqueous solution of sodium hydroxide was added to make the mixture alkaline. Sodium bicarbonate (6 g) was then added and the mixture was stirred at 100°C for 1 hour. Activated carbon was added to the reaction mixture, followed by Celite filtration. To the filtrate, carbon disulfide (2.70 ml) was added, followed by heating to about 50°C. Stirring was then conducted for 1.5 hours. After cooling to room temperature, the reaction mixture was made acidic with 1N

hydrochloric acid. Colorless powder thus precipitated was collected by filtration and dried, whereby the title compound (1.30 g, 14%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 7.28 (1H, d,  $J=8.3\text{Hz}$ ),

5 7.45 (1H, dd,  $J=8.3, 2.0\text{Hz}$ ), 7.86 (1H, d,  $J=2.0\text{Hz}$ ).

MS (FAB)  $m/z$ : 202  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 204  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

Elementary analysis for  $\text{C}_7\text{H}_4\text{ClNS}_2$

Calculated: C, 41.68; H, 2.00; Cl, 17.58; N, 6.94; S, 31.80.

10 Found: C, 41.64; H, 2.13; Cl, 17.83; N, 6.94; S, 31.70.

[Referential Example 146] 1-tert-Butoxycarbonyl-4-[(5-chloroenzothiazol-2-yl)sulphenyl]piperazine

At room temperature, tert-butyl 1-piperazine  
15 carboxylate (5.58 g), 5-chloro-2-mercaptobenzothiazole (1.21 g) and sodium hydroxide (0.48 g) were dissolved in water (25 ml), followed by the dropwise addition of an aqueous solution (25 ml) containing iodine (1.53 g) and potassium iodide (1.65 g). The colorless crystals so  
20 precipitated were collected by filtration, washed with water and dried under reduced pressure, whereby the title compound (1.1 g, 48%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48 (9H, s), 3.24 (4H, br), 3.58 (4H, br s),

7.26 (1H, m), 7.70 (1H, d,  $J=8.3\text{Hz}$ ), 7.81 (1H, s).

25 MS (FAB)  $m/z$ : 386  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 388  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 147] 1-tert-Butoxycarbonyl-4-[(6-chlorobenzothiazol-2-yl)sulphenyl]piperazine

In the same manner as in Referential Example 146, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48(9H,s), 3.24(4H,br s), 3.58(4H,br s), 7.37(1H,dd,J=8.8,2.0Hz), 7.73(1H,d,J=8.8Hz), 7.77(1H,d,J=2.0Hz).

MS (FAB)  $m/z$ : 386  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 388  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 [Referential Example 148] 1-tert-Butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulfonyl]piperazine

At room temperature, 1-tert-butoxycarbonyl-4-[(5-chlorobenzothiazol-2-yl)sulphenyl]piperazine (1.10 g) and potassium carbonate (1.30 g) were suspended in a mixed solvent of ethanol (30 ml) and water (10 ml), followed by the dropwise addition of a solution of 3-chloroperbenzoic acid (2.11 g) in ethanol (25 ml) at 0°C. The reaction mixture was heated to room temperature and stirred for 24 hours. Sodium thiosulfate and ethyl acetate were added to separate the organic layer. The organic layer thus obtained was dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent was purified by chromatography on a silica gel column (dichloromethane ~ 2% methanol - dichloromethane), whereby the title compound (293 mg, 25%) was obtained.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.43(9H,s), 3.35-3.43(4H,m), 3.51-

3.58(4H,m), 7.55(1H,dd,J=8.8,1.5Hz), 7.90(1H,d,J=8.8Hz),  
8.18(1H,d,J=1.5Hz).

MS (FAB) m/z: 418 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 420 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 149] 1-tert-Butoxycarbonyl-4-[(6-  
5 chlorobenzothiazol-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 148, the  
title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.43(9H,s), 3.35-3.43(4H,m), 3.50-  
3.58(4H,m), 7.59(1H,dd,J=8.8,2.0Hz), 7.97(1H,d,J=2.0Hz),  
10 8.10(1H,d,J=8.8Hz).

MS (FAB) m/z: 418 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 420 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

In the same manner as in Referential Example 35,  
compounds shown in Referential Examples 150 and 151 were  
synthesized, respectively.

15 [Referential Example 150] 1-[(5-Chlorobenzothiazol-2-  
yl)sulfonyl]piperazine hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.23(4H,br s), 3.56(4H,br s),  
7.78(1H,dd,J=8.8,2.0Hz), 8.39-8.43(2H,m).

MS (FAB) m/z: 318 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 320 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

20 [Referential Example 151] 1-[(6-Chlorobenzothiazol-2-  
yl)sulfonyl]piperazine hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.21-3.27(4H,m), 3.52-3.57(4H,m),  
7.79(1H,dd,J=8.8,2.0Hz), 8.28(1H,d,J=8.8Hz),  
8.53(1H,d,J=2.0Hz).

25 MS (FAB) m/z: 318 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 320 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for  $C_{11}H_{12}ClN_3O_2S_2 \cdot 1.05HCl \cdot 0.5H_2O$

Calculated: C, 36.19; H, 3.88; Cl, 19.91; N, 11.51;

S, 17.57.

Found: C, 36.19; H, 4.10; Cl, 20.08; N, 11.50;

5 S, 17.19.

In the same manner as in Referential Example 1, compounds shown in Referential Examples 152 to 155 were synthesized, respectively.

[Referential Example 152] 1-[(5-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazine hydrochloride

$^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.20(4H,br), 3.45(4H,br), 7.62(1H,d,J=8.8Hz), 7.76(1H,s), 7.85(1H,d,J=8.8Hz), 7.96(1H,s), 9.41(1H,br).

MS (FAB) m/z: 301 [(M+H) $^+$ , Cl $^{35}$ ], 303 [(M+H) $^+$ , Cl $^{37}$ ].

15 Elementary analysis for  $C_{12}H_{13}ClN_2O_3S \cdot HCl \cdot 0.1H_2O$

Calculated: C, 42.51; H, 4.22; Cl, 20.91; N, 8.26; S, 9.46.

Found: C, 42.38; H, 4.33; Cl, 20.92; N, 8.18; S, 9.58.

[Referential Example 153] 1-[(6-Chlorobenzo[b]furan-2-yl)sulfonyl]piperazine hydrochloride

20  $^1H$ -NMR (DMSO- $d_6$ )  $\delta$ : 3.20(4H,t,J=4.9Hz), 3.42(4H,t,J=4.9Hz), 7.51(1H,d,J=7.8Hz), 7.82(1H,s), 7.89(1H,d,J=7.8Hz), 9.18(1H,br).

MS (FAB) m/z: 301 [(M+H) $^+$ , Cl $^{35}$ ], 303 [(M+H) $^+$ , Cl $^{37}$ ].

Elementary analysis for  $C_{12}H_{13}ClN_2O_3S \cdot HCl \cdot 0.5H_2O$

25 Calculated: C, 41.63; H, 4.37; Cl, 20.48; N, 8.09; S, 9.26.

Found: C, 41.54; H, 4.32; Cl, 20.49; N, 7.90; S, 9.07.

[Referential Example 154] 1-[(5-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazine hydrochloride

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.20-3.50 (8H, m),

5 7.64 (1H, dd, J=8.8, 2.0 Hz), 8.12 (1H, s), 8.20 (1H, s),

8.23 (1H, d, J=8.8 Hz), 9.22 (2H, br s).

MS (FAB) m/z: 317 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 319 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>12</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>S<sub>2</sub>·HCl·1.6H<sub>2</sub>O

Calculated: C, 37.72; H, 4.54; Cl, 18.56; N, 7.33; S,

10 16.78.

Found: C, 37.56; H, 4.67; Cl, 18.72; N, 7.17; S,

16.56.

[Referential Example 155] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperazine hydrochloride

15 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.20-3.38 (8H, m),

7.59 (1H, dd, J=8.8, 2.0 Hz), 8.10 (1H, d, J=8.8 Hz), 8.16 (1H, s),

8.36 (1H, d, J=8.8 Hz), 9.29 (2H, br s).

MS (FAB) m/z: 317 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 319 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

Elementary analysis for C<sub>12</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub>S<sub>2</sub>·HCl

20 Calculated: C, 40.80; H, 3.99; Cl, 20.07; N, 7.93;

S, 18.15.

Found: C, 40.64; H, 4.04; Cl, 20.06; N, 7.90;

S, 17.91.

[Referential Example 156] 1-[(5-Bromopyrimidin-2-

25 yl)carbonyl]-4-[(6-chloronaphthalen-2-



yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.10-3.13 (2H,m), 3.22-3.25 (2H,m), 3.49-  
5 3.53 (2H,m), 3.90-3.94 (2H,m), 7.59 (1H,dd,J=8.8,2.0Hz),  
7.75 (1H,dd,J=8.8,1.5Hz), 7.91-7.95 (3H,m), 8.30 (1H,br s),  
8.82 (2H,s).

MS (FAB) m/z: 495 [(M+H)<sup>+</sup>, Cl<sup>35</sup> and Br<sup>79</sup>], 497 [(M+H)<sup>+</sup>, Cl<sup>35</sup>  
and Br<sup>81</sup>, Cl<sup>37</sup> and Br<sup>79</sup>], 499 [(M+H)<sup>+</sup>, Cl<sup>37</sup> and Br<sup>81</sup>].

10 [Referential Example 157] 1-[(5-Bromopyrimidin-2-  
yl)carbonyl]-4-[(6-chlorobenzothien-2-  
yl)sulfonyl]piperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.19-3.23 (2H,m), 3.29-3.33 (2H,m), 3.53-  
3.56 (2H,m), 3.93-3.97 (2H,m), 7.46 (1H,dd,J=8.8,1.5Hz),  
15 7.77 (1H,s), 7.83 (1H,d,J=8.8Hz), 7.88 (1H,d,J=1.5Hz),  
8.84 (2H,s).

MS (FAB) m/z: 501 [(M+H)<sup>+</sup>, Cl<sup>35</sup> and Br<sup>79</sup>], 503 [(M+H)<sup>+</sup>, Cl<sup>35</sup>  
and Br<sup>81</sup>, Cl<sup>37</sup> and Br<sup>79</sup>], 505 [(M+H)<sup>+</sup>, Cl<sup>37</sup> and Br<sup>81</sup>].

Elementary analysis for C<sub>17</sub>H<sub>14</sub>BrClN<sub>4</sub>O<sub>3</sub>S<sub>2</sub>

20 Calculated: C, 40.69; H, 2.81; N, 11.17; S, 12.78.

Found: C, 40.90; H, 2.87; N, 10.92; S, 12.87.

[Referential Example 158] 1-Benzyl-4-tert-  
butoxycarbonylpiperazine

In acetonitrile (80 ml), tert-butyl 1-piperazine  
25 carboxylate (2.50 g) was dissolved. Under ice cooling,

benzyl bromide (1.59 ml) and triethylamine (1.87 ml) were added dropwise to the resulting solution, followed by stirring at room temperature for 90 minutes. After the solvent was distilled off under reduced pressure, distilled water and dichloromethane were added to the residue to separate the organic layer. The organic layer was washed with saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:20 to 1:5), whereby the title compound (3.12 g, 84%) was obtained as colorless powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45(9H,s), 2.38(4H,t,J=4.9Hz), 3.42(4H,t,J=4.8Hz), 3.51(2H,s), 7.25-7.29(1H,m), 7.30-7.33(4H,m).

MS (EI)  $m/z$ : 276 $\text{M}^+$ .

[Referential Example 159] 1-Benzylpiperazine hydrochloride

To 1-benzyl-4-tert-butoxycarbonylpiperazine (3.12 g), saturated ethanol hydrochloride was added, followed by stirring for 90 minutes at room temperature. The solvent was distilled off under reduced pressure, followed by drying, whereby the title compound (2.73 g, 97%) was obtained as white powder.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.05-3.67(9H,m), 4.38(2H,br), 7.35-7.70(5H,m), 9.61(1H,br).

MS (EI) m/z: 176M<sup>+</sup>.

Elementary analysis for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>·2HCl·0.2H<sub>2</sub>O

Calculated: C, 52.27; H, 7.34; Cl, 28.05; N, 11.27.

Found: C, 52.04; H, 7.36; Cl, 27.89; N, 11.24.

5 [Referential Example 160] 1-Benzyl-4-sulfamoylpiperazine

Chlorosulfonyl isocyanate (0.35 ml) was dissolved in dichloromethane (5 ml). Under ice cooling, tert-butanol (0.21 ml) was added dropwise to the resulting solution, followed by stirring for 30 minutes. After the reaction mixture was added dropwise to a solution of 1-benzylpiperazine dihydrochloride (0.25 g) in dichloromethane (20 ml) under ice cooling, triethylamine (0.28 ml) was added. The mixture was stirred for 30 minutes under ice cooling and then at room temperature for 15 1 hour. Distilled water and dichloromethane were added to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol : 20 dichloromethane = 1:50 to 1:25), whereby 1-benzyl-[4-(N-tert-butoxycarbonyl)sulfamoyl]piperazine was obtained as colorless powder. To the resulting powder, saturated solution of hydrochloride in ethanol was added and the mixture was stirred at room temperature for 1 hour. After 25 the solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium bicarbonate and

dichloromethane were added to the residue to separate the organic layer. The resulting organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (0.26 g, quant.) was obtained as colorless powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.58(4H,t,J=4.9Hz), 3.22(4H,t,J=4.9Hz), 3.56(2H,s), 4.33(2H,br), 7.27-7.36(5H,m).

MS (EI)  $m/z$ : 255 $\text{M}^+$ .

[Referential Example 161] 3,4-Bis(bromomethyl)-1-chlorobenzene

In acetonitrile (500 ml), 1-chloro-3,4-dimethylbenzene (20.0 ml) was dissolved and to the resulting solution, N-bromosuccinimide (53.0 g) and azoisobutyronitrile (1.20 g) were added, followed by heating under reflux for 1 hour.

After cooling, the solvent was distilled off under reduced pressure and dichloromethane was then added to the residue. From the resulting mixture, the precipitate was filtered off. The filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane), whereby the title compound (41.5 g, 93%) was obtained as a colorless oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.59(2H,s), 4.61(2H,s), 7.27-7.36(3H,m).

MS (EI)  $m/z$ : 295 $\text{M}^+$ .

[Referential Example 162] 1-Benzyl-4-[(5-chloroisindol-2-yl)sulfonyl]piperazine

In ethanol (5 ml), 1-benzyl-4-sulfamoylpiperazine (251 mg) was dissolved. To the resulting solution, 3,4-bis(bromomethyl)-1-chlorobenzene (293 mg) and potassium carbonate (204 mg) were added, followed by heating under reflux for 3.5 hours. After cooling, the precipitate was filtered off. The filtrate was then distilled under reduced pressure and the residue was purified by chromatography on a silica gel column (dichloromethane ~ ethanol : dichloromethane = 1:100), whereby the title compound (222 mg, 58%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.37-2.58(4H,m), 3.24-3.41(4H,m), 3.53(2H,s), 4.64(4H,m), 7.13-7.34(8H,m).

MS (FAB)  $m/z$ : 392  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 394  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 163] 1-[(5-Chloroisindol-2-yl)sulfonyl]piperazine

To a solution of 1-benzyl-4-[(5-chloroisindol-2-yl)sulfonyl]piperazine (222 mg) in 1,2-dichloroethane (20 ml), 1-chloroethyl chloroformate (81 mg) was added under ice cooling. The resulting mixture was stirred for 15 minutes and then heated under reflux for 1 hour. After cooling, anhydrous methanol was added to the residue obtained by distilling off the solvent under reduced pressure. The mixture was heated under reflux for 11 hours. After cooling, the residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (ethanol :

dichloromethane = 1:50 to 1:10), whereby the title compound (120 mg, 70%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.96 (4H, t,  $J=4.4\text{Hz}$ ), 3.09-3.22 (1H, br), 3.30 (4H, t,  $J=4.4\text{Hz}$ ), 4.65 (4H, m), 7.14-7.35 (3H, m).

5 MS (FAB)  $m/z$ : 302  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 304  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 164] 1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroisoindol-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the title compound was obtained.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.35 (2H, t,  $J=4.9\text{Hz}$ ), 3.44 (2H, t,  $J=4.9\text{Hz}$ ), 3.49 (2H, t,  $J=4.9\text{Hz}$ ), 3.91 (2H, t,  $J=4.9\text{Hz}$ ), 4.65-4.68 (4H, m), 7.17 (1H, d,  $J=8.3\text{Hz}$ ), 7.23 (1H, s), 7.28 (1H, m), 8.88 (2H, s).

MS (EI)  $m/z$ : 486 $\text{M}^+$ .

[Referential Example 165] 2-(Furan-2-yl)-5-(pyridin-4-yl)pyrazine

At room temperature, 2-chloro-5-(furan-2-yl)pyrazine (N. Sato, J. Heterocyclic Chem., 19, 407 (1982)) (1.00 g) and (pyridin-4-yl)boronic acid (1.09 g) were suspended in a mixed solvent of dimethoxyethane (50 ml) and methanol (50 ml), followed by the successive addition of tetrakis(triphenylphosphine)palladium (0) (640 mg) and cesium fluoride (5.55 g). The resulting mixture was heated under reflux for 16 hours. After cooling, the reaction mixture was concentrated. Dichloromethane and water were added to the concentrate to separate the organic layer.

The organic layer was dried over anhydrous sodium sulfate, treated with activated carbon and filtered through Celite. After the filtrate was concentrated to about 5 ml, petroleum ether (50 ml) was added to the concentrate.

5 Yellow crystalline powder thus precipitated was collected by filtration and dried, whereby the title compound (716 mg, 58%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 6.62 (1H, dd,  $J=3.4, 2.0\text{Hz}$ ),

7.23 (1H, d,  $J=3.4\text{Hz}$ ), 7.65 (1H, d,  $J=2.0\text{Hz}$ ), 7.94 (2H, d,  $J=6.4\text{Hz}$ ),

10 8.77 (2H, d,  $J=6.4\text{Hz}$ ), 9.03 (1H, d,  $J=1.5\text{Hz}$ ), 9.07 (1H, d,  $J=1.5\text{Hz}$ ).

MS (FAB)  $m/z$ : 224 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 166] 5-(Pyridin-4-yl)pyrazine-2-carboxylic acid

At room temperature, potassium permanganate (700 mg) and trioctylmethylammonium chloride (one drop) were  
15 dissolved in a mixed solvent of water (20 ml) and benzene (20 ml). To the resulting solution, 2-(furan-2-yl)-5-(pyridin-4-yl)pyrazine (700 mg) was added in portions, followed by stirring at room temperature for 17 hours.  
20 After ethanol was added to the reaction mixture to decompose excess potassium permanganate, the solvent was distilled off. To the residue, water (100 ml) was added and the mixture was filtered through Celite. To the filtrate, 1N hydrochloric acid was added to adjust its pH  
25 to 6. The solvent was distilled off until the precipitation of colorless crystals. The colorless

crystals were collected by filtration, whereby the title compound (491 mg, 79%) was obtained.

$^1\text{H}$ -NMR (DMSO- $d_6$  with one drop of TEA)  $\delta$ :

8.61(2H,d,J=5.9Hz), 9.04(2H,d,J=5.9Hz), 9.37(1H,s),  
5 9.66(1H,s).

MS (FAB)  $m/z$ : 202 ( $M+H$ ) $^+$ .

Elementary analysis for  $\text{C}_{10}\text{H}_7\text{N}_3\text{O}_2 \cdot 0.4\text{H}_2\text{O}$

Calculated: C, 57.64; H, 3.77; N, 20.16.

Found: C, 57.77; H, 3.79; N, 20.33.

10 [Referential Example 167] 4-(3-Methylpyridin-4-yl)benzoic acid

In the same manner as in Referential Example 2, the title compound was obtained.

$^1\text{H}$ -NMR (DMSO- $d_6$ )  $\delta$ : 2.41(3H,s), 7.68(2H,d,J=8.3Hz),  
15 7.93(1H,d,J=5.9Hz), 8.12(2H,d,J=8.3Hz), 8.85(1H,d,J=5.9Hz),  
8.95(1H,s).

[Referential Example 168] 4-Amidinobenzoic acid

In ethanol (250 ml), 4-cyanobenzoic acid (10 g) was suspended. Under ice cooling, a hydrochloric acid gas was introduced into the resulting suspension for 4 hours.  
20 After heating to room temperature, the reaction mixture was hermetically sealed and then allowed to stand for 18 hours. The reaction mixture was concentrated to dryness under reduced pressure. The residue was suspended in  
25 ethanol (250 ml) again, followed by the introduction of an



ammonia gas for 4 hours under ice cooling for saturation. After heating to room temperature, the reaction mixture was hermetically sealed and allowed to stand for 3 days. To the residue obtained by distilling off the solvent under reduced pressure, dilute hydrochloric acid was added to make the residue acidic, followed by concentration. The residue was purified by chromatography through a synthetic adsorbent ("Diaion HP-20" (trade name); water ~ 20% acetonitrile - water). The crude purified product so obtained was dissolved in 20% methanol - dichloromethane and the resulting solution was purified by chromatography on a silica gel column (20% methanol - dichloromethane). To the resulting fraction, solution of hydrochloride in ethanol was added and the mixture was concentrated. From the concentrate, colorless crystal powder was collected by filtration and dried, whereby ethyl 4-amidinobenzoate hydrochloride (5.25 g) was obtained as a crude purified product.

In 1N hydrochloric acid (100 ml), the resulting ethyl 4-amidinobenzoate hydrochloride (3.00 g) was dissolved at room temperature, followed by heating under reflux for 2 hours. The solvent was then distilled off under reduced pressure. Colorless crystalline powder so precipitated was collected by filtration and washed with a small amount of tetrahydrofuran, whereby the title compound (2.69 g, 94%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 7.91 (2H, d,  $J=8.3\text{Hz}$ ), 8.12 (2H, d,  $J=8.3\text{Hz}$ ), 9.21 (2H, br s), 9.49 (2H, br s), 13.50 (1H, br s).

MS (FAB)  $m/z$ : 165 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_8\text{H}_8\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$

5 Calculated: C, 43.95; H, 5.07; Cl, 16.22; N, 12.81.

Found: C, 44.08; H, 5.02; Cl, 16.00; N, 12.71.

[Referential Example 169] Ethyl 4-(4,5-dihydroimidazol-2-yl)benzoate

10 In ethanol (250 ml), 4-cyanobenzoic acid (5.00 g) was suspended. A hydrochloric acid gas was blown into the resulting suspension for 4 hours under ice cooling, followed by heating to room temperature. The reaction mixture was hermetically sealed and allowed to stand for 18 hours, followed by concentration to dryness under reduced  
15 pressure. To the residue, diethyl ether was added. Colorless crystals thus precipitated were collected by filtration and dried, whereby ethyl 4-[1-(ethoxy)iminomethyl]benzoate hydrochloride (5.80 g, 66%) was obtained.

20 The resulting ethyl 4-[1-(ethoxy)iminomethyl]benzoate hydrochloride (2.00 g) was dissolved in ethanol (30 ml). Under ice cooling, ethylenediamine (0.52 ml) was added to the resulting solution, followed by heating to room temperature. The reaction mixture was stirred overnight.  
25 To the residue obtained by distilling off the solvent under reduced pressure, dilute hydrochloric acid was added to

make it acidic, followed by concentration again. The residue was purified by chromatography through a synthetic adsorbent ("Diaion HP-20", trade name; water ~ 50% acetonitrile-water). Solution of hydrochloride in ethanol was added to the resulting fraction and the mixture was concentrated. Colorless crystalline powder precipitated by the addition of tetrahydrofuran was collected by filtration and dried, whereby the title compound (1.63 g, 19%) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.35(3H,t,J=7.3Hz), 4.02(4H,s), 4.37(2H,q,J=7.3Hz), 8.17(2H,d,J=8.8Hz), 8.21(2H,d,J=8.8Hz), 11.08(2H,br s).

MS (FAB) m/z: 219 (M+H)<sup>+</sup>.

Elementary analysis for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>·HCl·0.2H<sub>2</sub>O

Calculated: C, 55.80; H, 6.01; Cl, 13.72; N, 10.84.

Found: C, 55.81; H, 5.99; Cl, 13.93; N, 11.00.

[Referential Example 170] 5-(4,5-Dihydroimidazol-2-yl)benzoic acid hydrochloride

In the same manner as in Referential Example 8, a reaction was effected using the ethyl 4-(4,5-dihydroimidazol-2-yl)benzoate as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 4.03(4H,s), 8.15(4H,s), 10.99(2H,br s).

MS (FAB) m/z: 191 (M+H)<sup>+</sup>.

Elementary analysis for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>·HCl·1.2H<sub>2</sub>O

Calculated: C, 48.38; H, 5.44; Cl, 14.28; N, 11.28.

Found: C, 48.37; H, 5.29; Cl, 14.64; N, 11.12.

[Referential Example 171] 4-(4-Methylphenyl)pyridine

In the same manner as in Referential Example 2, a  
5 reaction was effected, whereby the title compound was  
obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.42 (3H, s), 7.30 (2H, d,  $J=8.3\text{Hz}$ ),  
7.51 (2H, d,  $J=5.9\text{Hz}$ ), 7.55 (2H, d,  $J=8.3\text{Hz}$ ), 8.64 (2H, d,  $J=5.9\text{Hz}$ ).

[Referential Example 172] 2-Amino-4-(4-  
10 methylphenyl)pyridine

Under an argon gas, 4-(4-methylphenyl)pyridine (2.74  
g) was dissolved in *N,N*-dimethylaniline (10 ml), followed  
by the addition of sodium amide (1.40 g) at room  
temperature. After the resulting mixture was stirred at  
15  $110^\circ\text{C}$  for 2 days, the reaction mixture was cooled to room  
temperature. Brown powder precipitated by the addition of  
water was collected by filtration. The powder was further  
purified by chromatography on a silica gel column (ethyl  
acetate : toluene = 1:1). After concentration of the  
20 resulting fraction, hexane was added and powder thus  
precipitated was collected by filtration and dried, whereby  
the title compound (1.40 g, 47%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.40 (3H, s), 4.45 (2H, br s),  
6.69 (1H, d,  $J=1.5\text{Hz}$ ), 6.88 (1H, dd,  $J=5.4, 1.5\text{Hz}$ ),  
25 7.26 (2H, d,  $J=8.3\text{Hz}$ ), 7.49 (2H, d,  $J=8.3\text{Hz}$ ), 8.11 (1H, d,  $J=5.4\text{Hz}$ )

MS (FAB)  $m/z$ : 185 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 173] 2-Diacetylamino-4-(4-methylphenyl)pyridine

2-Amino-4-(4-methylphenyl)pyridine (1.27 g) was dissolved in dichloromethane (50 ml). Under ice cooling, N,N-diisopropylethylamine (1.80 ml) and acetyl chloride (735  $\mu$ l) were successively added dropwise to the resulting solution. After heating to room temperature, the reaction mixture was added again with N,N-diisopropylethylamine (0.90 ml) and acetyl chloride (800  $\mu$ l). The mixture was stirred for 18 hours. Methanol was added to the reaction mixture. Dilute hydrochloric acid and ethyl acetate were then added to the residue obtained by distilling off the solvent in order to separate the organic layer. The organic layer was dried over anhydrous magnesium sulfate, followed by concentration. The residue was dissolved in methanol. Crystals precipitated by the addition of water were collected by filtration and dried, whereby the title compound (1.39 g, 75%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.33(6H,s), 2.42(3H,s), 7.31(2H,d,J=8.3Hz), 7.43(1H,d,J=1.5Hz), 7.53-7.59(3H,m), 8.61(1H,d,J=4.9Hz).

MS (FAB)  $m/z$ : 269 ( $\text{M}+\text{H}$ ) $^+$ .

Elementary analysis for  $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$

Calculated: C, 71.62; H, 6.01; N, 10.44.

Found: C, 71.28; H, 5.98; N, 10.19.

[Referential Example 174] 4-(2-Acetylamino-4-methylphenyl)pyridine

yl)benzoic acid

In water (4 ml), anhydrous magnesium sulfate (161 mg) was dissolved. To the resulting solution, the 2-diacetylamino-4-(4-methylphenyl)pyridine (108 mg) was suspended. Potassium permanganate (223 mg) was added to the resulting suspension, followed by heating under reflux for 2 hours. After removal of manganese dioxide, dilute hydrochloric acid and dichloromethane were added to the filtrate to separate the water layer. The water layer was concentrated to about 20 ml and the crystals thus precipitated were collected by filtration and dried, whereby the title compound (64 mg, 62%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO}-d_6$ )  $\delta$ : 2.19(3H,s), 7.58(1H,d,J=5.9Hz), 7.87(2H,d,J=8.3Hz), 8.04(1H,s), 8.11(2H,d,J=8.3Hz), 8.33(1H,s), 8.43(1H,d,J=5.9Hz), 11.23(1H,br s).

MS (FAB)  $m/z$ : 257 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 175] Methyl 4-(2-aminopyridin-4-yl)benzoate

In the same manner as in Referential Example 9, a reaction was effected using the 4-(2-acetylamino-4-yl)benzoic acid as a starting material, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.95(3H,s), 4.53(2H,br s), 6.72(1H,d,J=1.5Hz), 6.90(1H,dd,J=5.4,1.5Hz), 7.65(2H,d,J=8.3Hz), 8.12(2H,d,J=8.3Hz), 8.16(1H,d,J=5.4Hz).

MS (FAB)  $m/z$ : 229 (M+H)<sup>+</sup>.

Elementary analysis for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>

Calculated: C, 68.41; H, 5.30; N, 12.27.

Found: C, 68.30; H, 5.27; N, 12.36.

5 [Referential Example 176] Methyl 4-[2-(N-tert-butoxycarbonylamino)pyridin-4-yl]benzoate

In the same manner as in Referential Example 10, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.50(9H,s), 3.89(3H,s),  
10 7.38(1H,dd,J=5.4,1.5Hz), 7.86(2H,d,J=8.3Hz),  
8.10(2H,d,J=8.3Hz), 8.14(1H,d,J=1.5Hz), 8.35(1H,d,J=5.4Hz),  
9.89(1H,br s).

[Referential Example 177] 4-[2-(N-tert-butoxycarbonylamino)pyridin-4-yl]benzoic acid

15 In the same manner as in Referential Example 11, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.49(9H,s), 7.38(1H,dd,J=5.4,1.0Hz),  
7.83(2H,d,J=8.3Hz), 8.07(2H,d,J=8.3Hz), 8.12(1H,d,J=1.0Hz),  
8.33(1H,d,J=5.4Hz), 9.93(1H,br s), 13.07(1H,br s).

20 [Referential Example 178]

1-[4-(2-Azidomethylpyridin-4-yl)benzoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (10 ml), 1-[(6-chloronaphthalen-2-yl)sulfonyl]-4-[4-(2-hydroxymethylpyridin-4-yl)benzoyl]piperazine (300 mg) was dissolved. To the  
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resulting solution, triphenylphosphine (301 mg) and carbon tetrabromide (572 mg) were added, followed by stirring at room temperature for 5 minutes. An aqueous solution of sodium bicarbonate and dichloromethane were added to separate the organic layer. After the organic layer was dried over anhydrous sodium sulfate, N,N-dimethylformamide (10 ml) was added and only dichloromethane was distilled off. To the N,N-dimethylformamide solution containing the bromo-compound, sodium azide (215 mg) was added, followed by stirring at an external temperature of about 100°C for 90 minutes. The reaction mixture was distilled under reduced pressure to remove the solvent. Dichloromethane and water were added to the residue to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ 2% methanol - dichloromethane), whereby the title compound (159 mg, 51%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.16(4H,br), 3.30-4.10(4H,br), 4.57(2H,s), 7.40-7.45(3H,m), 7.52(1H,s), 7.60(1H,dd,J=8.8 and 2.0Hz), 7.64(2H,d,J=8.3Hz), 7.76(1H,dd,J=8.3 and 1.5Hz), 7.90-7.96(3H,m), 8.31(1H,d,J=1.5Hz), 8.65(1H,d,J=5.4Hz).

MS (FAB)  $m/z$ : 547  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 549  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 179] Methyl 4-(2-methylpyridin-4-



yl)benzoate hydrochloride

In methanol (100 ml), 4-(2-methylpyridin-4-yl)benzoic acid hydrochloride (5.00 g) was dissolved. To the resulting solution, thionyl chloride (1.73 ml) was added dropwise, followed by heating under reflux for 3.5 hours. The reaction mixture was distilled to remove the solvent and pale brown crystals thus precipitated were washed with ethyl acetate, whereby the title compound (4.70 g, 89%) was obtained.

[Referential Example 180] Methyl 4-(2-bromomethylpyridin-4-yl)benzoate

In a mixed solution of carbon tetrachloride and an aqueous solution of sodium bicarbonate, the methyl 4-(2-methylpyridin-4-yl)benzoate hydrochloride (100 mg) was dissolved. The organic layer separated was dried over anhydrous sodium sulfate. After the insoluble matter was filtered off, N-bromosuccinic imide (68 mg) and 2,2'-azoisobutyronitrile (6 mg) were added to the filtrate, followed by heating under reflux for 1 hour. The reaction mixture was diluted with dichloromethane, washed with water and then dried over anhydrous sodium sulfate. The residue obtained by concentration under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (41 mg, 35%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.96(3H,s), 4.63(2H,s),

7.46 (1H, dd, J=4.9, 1.5Hz), 7.68 (1H, d, J=1.5Hz),  
7.71 (2H, d, J=8.3Hz), 8.16 (2H, d, J=8.3Hz), 8.69 (1H, d, J=4.9Hz).

Elementary analysis for  $C_{14}H_{12}BrNO_2$

Calculated: C, 54.92; H, 3.95; Br, 26.10; N, 4.58.

5 Found: C, 54.95; H, 3.96; Br, 25.85; N, 4.33.

[Referential Example 181] Methyl 4-(2-cyanomethylpyridin-4-yl)benzoate

In the same manner as in Referential Example 56, the title compound was obtained.

10  $^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 3.97 (3H, s), 4.03 (2H, s),  
7.51 (1H, d, J=5.4Hz), 7.67 (1H, s), 7.71 (2H, d, J=8.3Hz),  
8.17 (2H, d, J=8.3Hz), 8.67 (1H, d, J=5.4Hz).

Elementary analysis for  $C_{15}H_{12}N_2O_2$

Calculated: C, 71.42; H, 4.79; N, 11.10.

15 Found: C, 71.13; H, 4.82; N, 11.05.

[Referential Example 182] Methyl 4-[2-(2-aminoethyl)pyridin-4-yl]benzoate dihydrochloride

In methanol (5 ml), the methyl 4-(2-cyanomethylpyridin-4-yl)benzoate (190 mg) was dissolved.

20 The resulting solution was subjected to catalytic reduction by the addition of 10% palladium-carbon (190 mg) and concentrated hydrochloric acid (5 drops) at room temperature under normal pressure for 24 hours. After the removal of the catalyst by filtration, the filtrate was  
25 concentrated under reduced pressure. Ethyl acetate was added to the concentrate. Pale yellow crystals thus

precipitate were collected by filtration and then dried, whereby the title compound (141 mg, 57%) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 3.21-3.39 (4H, m), 3.90 (3H, s), 7.90-8.18 (8H, m), 8.76 (1H, d,  $J=5.4\text{Hz}$ ).

5 MS (FAB)  $m/z$ : 257 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 183] Methyl 4-[2-[2-(tert-butoxycarbonylamino)ethyl]pyridin-4-yl]benzoate

In the same manner as in Referential Example 10, the title compound was obtained.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.43 (9H, s), 3.07 (2H, t,  $J=6.4\text{Hz}$ ), 3.60 (2H, q,  $J=6.4\text{Hz}$ ), 3.96 (3H, s), 5.14 (1H, br s), 7.39 (1H, dd,  $J=5.4$  and  $1.5\text{Hz}$ ), 7.41 (1H, br s), 7.70 (2H, d,  $J=8.3\text{Hz}$ ), 8.15 (2H, d,  $J=8.3\text{Hz}$ ), 8.62 (1H, d,  $J=5.4\text{Hz}$ ).  
MS (FAB)  $m/z$ : 357 ( $\text{M}+\text{H}$ ) $^+$ .

15 [Referential Example 184]

1-[(6-Chloronaphthalen-2-yl)sulfonyl]-6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine

At room temperature, 2-methoxycarbonylpyrazine (1.00 g) was dissolved in methanol. The resulting solution was subjected to catalytic reduction by the addition of 10% palladium-carbon (100 mg) for 2 hours under normal pressure. After the removal of the catalyst by filtration, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (5% methanol-dichloromethane), whereby 6-

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methoxycarbonyl-1,2,3,4-tetrahydropyrazine (880 mg, 86%) was obtained as a yellow oil.

The resulting 6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine (440 mg) was dissolved in dichloromethane (5 ml), followed by the addition of N,N-diisopropylethylamine (594  $\mu$ l) and 6-(chloronaphthalen-2-yl)sulfonyl chloride (810 mg). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was washed with an aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and then concentrated. The residue thus obtained was purified by chromatography on a silica gel column (2% methanol - dichloromethane), whereby the title compound (279 mg, 25%) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.32(4H,s), 3.71(3H,s), 4.68(1H,br s), 7.43(1H,d,J=6.8Hz), 7.55(1H,dd,J=8.8,2.0Hz), 7.86-7.94(3H,m), 8.19(1H,dd,J=8.8,2.0Hz), 8.54(1H,br s).  
MS (FAB) m/z: 367 [(M+H) $^+$ ,  $\text{Cl}^{35}$ ], 369 [(M+H) $^+$ ,  $\text{Cl}^{37}$ ].

Elementary analysis for  $\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_4\text{S}$

Calculated: C, 52.39; H, 4.12; N, 7.64.

Found: C, 52.31; H, 4.21; N, 7.55.

[Referential Example 185] 1-(4-Bromobenzoyl)-6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine

In the same manner as in Referential Example 184, 6-methoxycarbonyl-1,2,3,4-tetrahydropyrazine was obtained, followed by reaction with 4-bromobenzoyl chloride, whereby

the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.20-3.70 (7H, m), 4.71 (1H, br s),  
7.16 (1H, d,  $J=6.4\text{Hz}$ ), 7.48 (4H, s).

MS (FAB)  $m/z$ : 325  $[(\text{M}+\text{H})^+, \text{Br}^{79}]$ , 327  $[(\text{M}+\text{H})^+, \text{Br}^{81}]$ .

5 [Referential Example 186] 4-(4-Bromobenzoyl)-1-[(6-chloronaphthalen-2-yl)sulfonyl-5-methoxycarbonyl-1,2,3,4-tetrahydropyrazine

In the same manner as in Example A-165, the title compound was obtained.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.40-3.90 (7H, m), 7.33 (2H, d,  $J=8.3\text{Hz}$ ),  
7.48 (2H, d,  $J=8.3\text{Hz}$ ), 7.60-7.66 (2H, m),  
7.79 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.92-7.99 (3H, m), 8.43 (1H, br s).  
MS (FAB)  $m/z$ : 549  $[(\text{M}+\text{H})^+, \text{Br}^{79}]$ , 551  $[(\text{M}+\text{H})^+, \text{Br}^{81}]$ .

Elementary analysis for  $\text{C}_{23}\text{H}_{18}\text{BrClN}_2\text{O}_5\text{S}$

15 Calculated: C, 50.24; H, 3.30; N, 5.10; S, 5.83.

Found: C, 50.34; H, 3.37; N, 5.05; S, 5.81.

[Referential Example 187] 4-[3-(Aminomethyl)phenyl]benzoic acid hydrochloride

20 In the same manner as in Referential Example 2, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 4.11 (2H, s), 7.49-7.58 (2H, m),  
7.76 (1H, d,  $J=6.8\text{Hz}$ ), 7.83 (2H, d,  $J=8.8\text{Hz}$ ), 7.92 (1H, br s),  
8.05 (2H, d,  $J=8.3\text{Hz}$ ).

[Referential Example 188]

25 4-[3-[(tert-Butoxycarbonylamino)methyl]phenyl]benzoic acid

In the same manner as in Referential Example 10, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48 (9H, s), 4.41 (2H, d, J=5.4Hz),  
4.94 (1H, br s), 7.28-7.37 (1H, m), 7.44 (1H, t, J=7.3Hz), 7.50-  
5 7.60 (2H, m), 7.68 (2H, d, J=8.3Hz), 8.10-8.23 (2H, m).

[Referential Example 189] Ethyl 2,5-dihydro-5-oxo-3-(pyridin-4-yl)-1,2,4-triazine-6-carboxylate

In ethanol (20 ml), 4-pyridinecarboxyamidrazone (1.48 g) was dissolved. To the resulting solution, diethyl  
10 ketomalonate (1.65 ml) was added dropwise at room temperature, followed by stirring for 13 hours. After heating under reflux for 4 hours, the reaction mixture was cooled. Yellow crystals thus precipitated were collected by filtration and dried, whereby the title compound (1.50  
15 g, 56%) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.31 (3H, t, J=7.3Hz), 4.36 (2H, q, J=7.3Hz),  
7.98 (2H, d, J=6.3Hz), 8.86 (2H, d, J=6.3Hz).

MS (FAB) m/z: 247 (M+H)<sup>+</sup>.

Elementary analysis for C<sub>11</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub>·0.2H<sub>2</sub>O

20 Calculated: C, 52.88; H, 4.20; N, 22.43.

Found: C, 52.78; H, 4.36; N, 22.66.

[Referential Example 190] 2,5-Dihydro-5-oxo-3-(pyridin-4-yl)-1,2,4-triazine-6-carboxylic acid

In the same manner as in Referential Example 11, the  
25 title compound was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$  (containing a small amount of trifluoroacetic acid))  $\delta$ : 8.31(2H,d,J=6.4Hz), 8.86(2H,d,J=6.4Hz).

MS (FAB)  $m/z$ : 218 ( $\text{M}+\text{H}$ ) $^+$ .

5 Elementary analysis for  $\text{C}_9\text{H}_6\text{N}_4\text{O}_3 \cdot 0.2\text{H}_2\text{O}$

Calculated: C, 48.74; H, 2.91; N, 25.26.

Found: C, 48.58; H, 2.87; N, 25.21.

[Referential Example 191] 2,6-Bis(methoxycarbonylmethyl)-1,4-dibenzylpiperazine

10 In a shield tube, bis(3-methoxycarbonyl-2-propylenyl)benzylamine (104 mg) and benzylamine (60.0  $\mu\text{l}$ ) were dissolved in methanol (5 ml). After the tube was hermetically sealed, the resulting solution was stirred under heat at an external temperature of about 100 to 110°C

15 for 63 hours. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (n-hexane : ethyl acetate = 3:1), whereby the title compound (123 mg, 88%) was obtained as a yellow oil.

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.25-2.60(8H,each m), 3.15-3.85(12H,m), 7.15-7.30(10H,m).

MS (FAB)  $m/z$ : 411 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 192] cis-2,6-

Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

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trans-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In methanol (70 ml) and hydrochloric acid (570  $\mu$ l), 2,6-bis(methoxycarbonylmethyl)-1,4-dibenzylpiperazine (1.33 g) was dissolved. To the resulting solution, palladium hydroxide (149 mg) was added, followed by catalytic hydrogenation at room temperature for 4 hours. After the removal of the catalyst by filtration, the residue was distilled under reduced pressure to remove the solvent.

Dichloromethane (70 ml) and N,N-diisopropylethylamine (2.70 ml) were added to the resulting residue to dissolve the latter in the former, followed by the addition of (6-chloronaphthalen-2-yl)sulfonyl chloride (495 mg). The mixture was stirred for 3 hours under stirring. To the reaction mixture, (6-chloronaphthalen-2-yl)sulfonyl chloride (200 mg) and N,N-diisopropylethylamine (180  $\mu$ l) were added. The resulting mixture was stirred for 12.5 hours, while gradually heated to room temperature from an external temperature of about 0°C. Since the reaction was not completed, (6-chloronaphthalen-2-yl)sulfonyl chloride (101 mg) and N,N-diisopropylethylamine (90  $\mu$ l) were added further and the mixture was stirred for 4.5 hours while heated gradually to room temperature from an external temperature of about 0°C. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (5%



methanol - dichloromethane, n-hexane : ethyl acetate = 1:2), whereby the title compounds, cis-form (226 mg, 15%) and trans-form (1.07 g, 73%), were obtained, respectively, as pale yellow amorphous powder.

5 cis-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.00-2.10 (2H,m), 2.20-2.30 (2H,m), 2.35-2.45 (2H,m), 2.85 (1H,br), 3.20-3.30 (2H,m), 3.69 (6H,s), 3.70-3.80 (2H,m), 7.50-7.60 (1H,m), 7.70-7.80 (1H,m), 7.85-7.95 (3H,m), 8.30 (1H,s).

trans-2,6-Bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.40-2.60 (5H,m), 2.80-2.90 (2H,m), 3.10-3.20 (2H,m), 3.45-3.55 (2H,m), 3.69 (6H,s), 7.50-7.60 (1H,m), 7.70-7.80 (1H,m), 7.85-7.95 (3H,m), 8.29 (1H,s).

MS (FAB)  $m/z$ : 455  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 457  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 193] trans-2,6-

Bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

20 In dichloromethane (8 ml), the trans-2,6-bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (79.7 mg) was dissolved. Under ice cooling, N,N-diisopropylethylamine (68.0  $\mu\text{l}$ ) and a solution of 4-bromobenzoyl chloride (51.0 mg) in dichloromethane (2  
25 ml) were added to the resulting solution, followed by stirring at room temperature for 5.5 hours. Water was

added to the reaction mixture to separate the organic layer. The organic layer was washed with saturate aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent.

5 The residue was purified by chromatography on a silica gel column (n-hexane : ethyl acetate=1:1), whereby the title compound (113 mg, 98%) was obtained as pale yellow amorphous powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.80-2.90 (4H,m), 3.20-3.40 (4H,m),  
10 3.63 (6H,s), 4.20-4.30 (2H,m), 7.23 (2H,d,J=8.3Hz),  
7.50 (2H,d,J=8.3Hz), 7.55-7.65 (1H,m), 7.70-7.80 (1H,m), 7.90-  
7.95 (3H,m), 8.30 (1H,s).

MS (FAB) m/z: 637 [(M+H)<sup>+</sup>, Br<sup>79</sup>, Cl<sup>35</sup>], 639 [(M+H)<sup>+</sup>, Br<sup>79</sup>,  
Cl<sup>37</sup> and Br<sup>81</sup>, Cl<sup>35</sup>], 641 [(M+H)<sup>+</sup>, Br<sup>81</sup>, Cl<sup>37</sup>].

15 [Referential Example 194] cis-2,6-  
Bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 193, the title compound was obtained.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.40-2.75 (4H,m), 2.80-3.20 (2H,m), 3.55-  
4.00 (2H,m), 3.68 (6H,s), 4.20-4.40 (1H,m), 5.00-5.20 (1H,m),  
7.10-7.15 (2H,m), 7.45-7.55 (2H,m), 7.55-7.65 (1H,m), 7.70-  
7.80 (1H,m), 7.90-7.95 (3H,m), 8.30 (1H,s).

MS (FAB) m/z: 637 [(M+H)<sup>+</sup>, Br<sup>79</sup>, Cl<sup>35</sup>], 639 [(M+H)<sup>+</sup>, Br<sup>79</sup>,  
25 Cl<sup>37</sup> and Br<sup>81</sup>, Cl<sup>35</sup>], 641 [(M+H)<sup>+</sup>, Br<sup>81</sup>, Cl<sup>37</sup>].

[Referential Example 195] trans-2,6-Bis(carbamoylmethyl)-  
1-(4-bromobenzoyl)-4-[(6-chloronaphthalen-2-  
yl)sulfonyl]piperazine

In the same manner as in Example A-35, the title  
5 compound was obtained using trans-2,6-  
bis(methoxycarbonylmethyl)-1-(4-bromobenzoyl)-4-[(6-  
chloronaphthalen-2-yl)sulfonyl]piperazine as a starting  
material.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.5-2.65 (2H,m), 3.10-3.30 (4H,m), 3.40-  
10 3.50 (2H,m), 4.20-4.30 (2H,m), 6.34 (2H,broad s), 6.59 (2H,br  
s), 7.14 (2H,d,J=8.3Hz), 7.31 (2H,d,J=8.3Hz), 7.50-  
7.60 (1H,m), 7.65-7.75 (1H,m), 7.85-7.95 (3H,m), 8.26 (1H,s).

[Referential Example 196] (2-Methylpyridin-4-  
yl)tributyltin

15 Under an argon stream, diethyl ether (100 ml) was  
cooled to -70°C, followed by the dropwise addition of an n-  
butyl lithium-hexane solution (1.52M, 14.5 ml). To the  
reaction mixture, a diethyl ether solution (100 ml)  
containing the free form of 4-bromo-2-methylpyridine was  
20 added dropwise over 15 minutes, followed by the dropwise  
addition of a tetrahydrofuran solution (10 ml) containing  
tributyltin chloride (5.40 ml) slowly. After stirring at -  
70°C for 30 minutes, the reaction mixture was heated to  
room temperature and stirring was conducted for 1.5 hours.  
25 Water and aqueous ammonia were added to the reaction  
mixture and the reaction mixture was separated using

diethyl ether. The organic layer was dried over anhydrous magnesium sulfate, the filtrate was concentrated and the residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 29:1 → 19:1), whereby the title compound (3.63 g, colorless oil substance) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.89(9H,t,J=7.3Hz), 0.99-1.17(6H,m), 1.22-1.41(6H,m), 1.50-1.65(6H,m), 2.52(3H,s), 7.05-7.21(1H,m), 7.22(1H,s), 7.34-8.40(1H,m).

MS (FAB)  $m/z$ : 382[(M+H) $^+$ ,  $\text{Sn}^{118}$ ], 384[(M+H) $^+$ ,  $\text{Sn}^{120}$ ].

Preparation of the free form of 4-bromo-2-methylpyridine

By using an aqueous solution of sodium bicarbonate and diethyl ether, 4-bromo-2-methylpyridine hydrochloride (4.17 g) was separated. The organic layer was dried over anhydrous magnesium sulfate and concentrated. Benzene was added to the concentrate, followed by concentration again. The residue was dissolved in diethyl ether (100 ml) and the resulting solution was stored a diethyl ether solution.

[Referential Example 197] (3-Fluoropyridin-4-

yl)tributyltin

Under an argon stream, a solution of diisopropylamine (7.03 ml) in tetrahydrofuran (100 ml) was cooled to an internal temperature of  $-20^\circ\text{C}$ , followed by the dropwise addition of an *n*-butyl lithium-hexane solution (1.52M, 32.9 ml). After stirring at  $0^\circ\text{C}$  for 1 hour, the reaction mixture was cooled to  $-70^\circ\text{C}$ . A solution of 3-fluoropyridine

(4.3 ml) in tetrahydrofuran (25 ml) was added dropwise over 30 minutes. The reaction mixture was stirred at  $-70^{\circ}\text{C}$  for 5 hours. A solution of tributyltin chloride (13.5 ml) in tetrahydrofuran (25 ml) was added dropwise slowly and the reaction mixture was stirred for 2.5 hours. The reaction mixture was heated to room temperature and then, separated using diethyl ether and water. The organic layer was dried over anhydrous magnesium sulfate, the filtrate was concentrated and purified by chromatography on a silica gel column (hexane : ethyl acetate = 19:1), whereby the title compound (colorless oil, 18.17 g) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.89(9H,t,J=7.3Hz), 1.06-1.27(6H,m), 1.28-1.40(6H,m), 1.43-1.70(6H,m), 7.25-7.42(1H,m), 8.30-8.40(2H,m).

MS (FAB)  $m/z$  386[(M+H) $^+$ ,  $\text{Sn}^{118}$ ], 388[(M+H) $^+$ ,  $\text{Sn}^{120}$ ].

In the same manner as in Referential Example 196, compounds shown in Referential Examples 198 to 199 were synthesized.

[Referential Example 198] (2,6-Dimethylpyridin-4-yl)tributyltin

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.89(9H,t,J=7.3Hz), 0.95-1.15(6H,m), 1.26-1.38(6H,m), 1.43-1.65(6H,m), 2.49(6H,s), 6.97-7.07(2H,m).

MS (FAB)  $m/z$  396[(M+H) $^+$ ,  $\text{Sn}^{118}$ ], 398[(M+H) $^+$ ,  $\text{Sn}^{120}$ ].

[Referential Example 199] (2,5-Dimethylpyridin-4-yl)tributyltin

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  0.89(9H,t, $J=7.3\text{Hz}$ ), 0.95-1.20(6H,m), 1.21-1.40(6H,m), 1.41-1.65(6H,m), 2.30(3H,s), 2.48(3H,s), 7.13(1H,s), 8.24(1H,s).

MS (FAB)  $m/z$  396[(M+H) $^+$ ,  $\text{Sn}^{118}$ ], 398[(M+H) $^+$ ,  $\text{Sn}^{120}$ ].

5 [Referential Example 200] 2,3-Dimethylpyridine N-oxide

In methylene chloride (200 ml) was dissolved 2,3-dimethylpyridine (9.50 g) and the resulting solution was cooled to 0°C. Metachloroperbenzoic acid (21.9 g) was added to the reaction mixture, followed by heating to room  
10 temperature. Stirring was conducted for 3 days. An aqueous solution of sodium sulfite was added and the resulting mixture was separated using methylene chloride (200 ml). The organic layer was dried over anhydrous magnesium sulfate, the filtrate was concentrated and the  
15 concentrate was purified by chromatography on a silica gel column (5% methanol - methylene chloride). Petroleum ether was added to the residue. Colorless powder so precipitated was collected by filtration, followed by drying, whereby the title compound (5.47 g) was obtained.

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.35(3H,s), 2.51(3H,s), 7.00-7.08(2H,m), 8.17(1H,d, $J=6.3\text{Hz}$ ).

MS (FAB)  $m/z$  124(M+H) $^+$ .

[Referential Example 201] 2,3-Dimethyl-4-nitropyridine N-oxide

In a mixed solvent of concentrated sulfuric acid (10 ml) and fuming nitric acid (10 ml) was dissolved 2,3-dimethylpyridine N-oxide (3.73 g) at 0°C. The resulting solution was stirred at 75°C for 1.5 hours and at 100°C for 15 minutes. The reaction mixture was charged in ice water, followed by neutralization with an aqueous solution of sodium hydroxide. The neutralized solution was separated using methylene chloride. The organic layer was dried over anhydrous magnesium sulfate and the filtrate was concentrated. Methylene chloride (1 ml) and diethyl ether (100 ml) were added to the residue. Pale yellow powder thus precipitated was collected by filtration and dried, whereby the title compound (3.31 g) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  2.57(3H,s), 2.58(3H,s),

7.71(1H,d,J=7.3Hz), 8.17(1H,d,J=7.3Hz).

MS (FAB)  $m/z$  169(M+H) $^+$ .

[Referential Example 202] 4-Bromo-2,3-dimethylpyridine

To 2,3-Dimethyl-4-nitropyridine N-oxide (3.00 g) which had been cooled to 0°C, added was acetyl bromide (18.0 ml), followed by stirring at 50°C for 20 minutes and then at 75°C for 15 minutes. The reaction mixture was charged in ice water and neutralized with an aqueous solution of ammonium carbonate. The neutralized solution was separated using methylene chloride. The organic layer was dried over anhydrous sodium sulfate and the filtrate was concentrated,

whereby a crudely purified product of 4-bromo-2,3-dimethylpyridine N-oxide was obtained.

The resulting product was dissolved in chloroform (50 ml), followed by cooling to 0°C. Phosphorus tribromide (5.16 ml) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was charged in ice water and neutralized with an aqueous solution of sodium bicarbonate. Methylene chloride was added to separate the neutralized solution. The organic layer was dried over anhydrous sodium sulfate, the filtrate was concentrated and the concentrate was purified by chromatography on a silica gel column (hexane : ethyl acetate = 19:1), whereby the title compound (1.90 g, 57%, pale yellow oil) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 2.40(3H,s), 2.59(3H,s),

7.34(1H,d,J=5.4Hz), 8.09(1H,d,J=5.4Hz).

MS (EI) m/z 185(M<sup>+</sup>, Br<sup>79</sup>), 187(M<sup>+</sup>, Br<sup>81</sup>).

[Referential Example 203] (2,3-Dimethylpyridin-4-yl)tributyltin

In the same manner as in Referential Example 196, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ 0.88(9H,t,J=7.3Hz), 1.01-1.18(6H,m), 1.27-1.37(6H,m), 1.41-1.61(6H,m), 2.31(3H,s), 2.50(3H,s), 7.07-7.20(1H,m), 8.19-8.24(1H,m).

MS (FAB) m/z 396[(M+H)<sup>+</sup>, Sn<sup>118</sup>], 398[(M+H)<sup>+</sup>, Sn<sup>120</sup>].



[Referential Example 204] 3,5-Dimethylpyridine N-oxide

In the same manner as in Referential Example 200, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.28(6H,s), 6.93(1H,s), 7.92(2H,s).

5 MS (FAB)  $m/z$ : 124 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 205] 3,5-Dimethyl-4-nitropyridine N-oxide

In the same manner as in Referential Example 201, the title compound was obtained.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.32(6H,s), 7.99(2H,s).

MS (FAB)  $m/z$ : 169 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 206] 4-Bromo-3,5-dimethylpyridine

In the same manner as in Referential Example 202, the title compound was obtained.

15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.38(6H,s), 8.23(2H,s).

MS (EI)  $m/z$ : 185( $\text{M}^+$ ,  $\text{Br}^{79}$ ), 187( $\text{M}^+$ ,  $\text{Br}^{81}$ ).

In the same manner as in Referential Example 196, the compounds shown in Referential Examples 207 to 211 were synthesized.

20 [Referential Example 207] (3,5-Dimethylpyridin-4-yl)tributyltin

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.88(9H,t,  $J=7.3\text{Hz}$ ), 1.04-1.21(6H,m),  
1.28-1.37(6H,m), 1.41-1.59(6H,m), 2.34(6H,s), 8.13-  
8.18(2H,m).

25 MS (FAB)  $m/z$ : 396 [ $(\text{M}+\text{H})^+$ ,  $\text{Sn}^{118}$ ], 398 [ $(\text{M}+\text{H})^+$ ,  $\text{Sn}^{120}$ ].

[Referential Example 208] (6-Methylpyridin-2-yl)tributyltin

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.88 (9H, t, J=7.3Hz), 1.01-1.18 (6H, m),  
1.26-1.37 (6H, m), 1.43-1.63 (6H, m), 2.54 (3H, s),  
5 6.95 (1H, d, J=7.3Hz), 7.18 (1H, d, J=7.3Hz), 7.36 (1H, t, J=7.3Hz).  
MS (FAB) m/z: 382 [(M+H)<sup>+</sup>, Sn<sup>118</sup>], 384 [(M+H)<sup>+</sup>, Sn<sup>120</sup>].

[Referential Example 209] (3-Methylpyridin-4-yl)tributyltin

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.89 (9H, t, J=7.3Hz), 1.02-1.20 (6H, m),  
10 1.27-1.37 (6H, m), 1.42-1.62 (6H, m), 2.35 (3H, s), 7.22-  
7.34 (1H, m), 8.28-8.38 (2H, m).  
MS (FAB) m/z: 382 [(M+H)<sup>+</sup>, Sn<sup>118</sup>], 384 [(M+H)<sup>+</sup>, Sn<sup>120</sup>].

[Referential Example 210] (5-Methylpyridin-2-yl)tributyltin

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.88 (9H, t, J=7.3Hz), 1.02-1.19 (6H, m),  
15 1.27-1.37 (6H, m), 1.43-1.61 (6H, m), 2.29 (3H, s), 7.27-  
7.33 (2H, m), 7.59 (1H, s).  
MS (FAB) m/z: 382 [(M+H)<sup>+</sup>, Sn<sup>118</sup>], 384 [(M+H)<sup>+</sup>, Sn<sup>120</sup>].

[Referential Example 211] (3-Methylpyridin-2-yl)tributyltin

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.87 (9H, t, J=7.3Hz), 1.05-1.23 (6H, m),  
1.27-1.38 (6H, m), 1.46-1.60 (6H, m), 2.36 (3H, s),  
7.02 (1H, dd, J=7.8 and 4.9Hz), 7.33 (1H, d, J=7.8Hz),  
8.54 (1H, d, J=4.9Hz).  
25 MS (FAB) m/z: 382 [(M+H)<sup>+</sup>, Sn<sup>118</sup>], 384 [(M+H)<sup>+</sup>, Sn<sup>120</sup>].

[Referential Example 212] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]piperidin-4-one

In N,N-dimethylformamide (10 ml) was suspended piperidin-4-one (monohydrochloric acid monohydrate, 1.54 g), followed by the addition of diisopropylethylamine (3.48 ml) and 6-chlorobenzo[b]thiophene-2-sulfonyl chloride (2.68 g). The resulting mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was then added to the residue, followed by washing with 1N hydrochloric acid. After extraction, the organic layer was dried over anhydrous sodium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (ethyl acetate : methylene chloride = 3:1), followed by washing with hexane, whereby the title compound (colorless prism crystals, 1.92 g) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.59(4H,d,J=6.4Hz), 3.55(4H,d,J=6.4Hz), 7.45(1H,dd,J=8.8,2.0Hz), 7.80-7.84(2H,m), 7.87(1H,d,J=2.0Hz).

MS (FAB) m/z: 330  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 332  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 213] 4-(4-Bromobenzylidene)-1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperidine

In a mixed solvent of tetrahydrofuran (10 ml) and ethanol (10 ml) was dissolved 4-bromobenzyl triphenylphosphonium bromide (512 mg). The resulting

solution was cooled to 0°C, followed by the successive addition of sodium hydride (60% in oil, 40 mg) and 1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperidin-4-one (297 mg). The resulting mixture was stirred at room temperature for 16 hours and at 50°C for 9 hours. Saturated aqueous NaCl solution and ethyl acetate were added to the reaction mixture to separate the same. The resulting organic layer was dried over anhydrous magnesium sulfate, the filtrate was concentrated and the residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby the title compound (colorless powder, 133 mg) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.48 (2H, d, J=5.9Hz), 2.57 (2H, d, J=5.9Hz), 3.16 (2H, d, J=5.9Hz), 3.28 (2H, d, J=5.9Hz), 6.25 (1H, s), 6.97 (2H, d, J=8.3Hz), 7.40-7.45 (3H, m), 7.73 (1H, s), 7.79 (1H, d, J=8.5Hz), 7.84 (1H, d, J=1.2Hz).

[Referential Example 214] 6-Bromobenzo[b]thiophene

To quinoline (45 ml) were added 6-bromobenzothiophene-2-carboxylic acid (14 g) and copper powder (874 mg), followed by stirring under heat at an oil temperature of 220°C for 2 hours. After the reaction mixture was allowed to cool down, ether was added and the copper powder was filtered off. The filtrate was washed with a 1N aqueous solution of hydrochloric acid, then with a 1N aqueous solution of sodium hydroxide and finally with saturated aqueous NaCl solution, followed by drying over anhydrous

sodium sulfate. The solvent was then distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane), whereby the title compound (5.56 g) was obtained as a pale yellow solid. In addition, the raw material (3.15 g) was recovered.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.29(1H,d,J=5.4Hz), 7.42(1H,d,J=5.4Hz), 7.46(1H,dd,J=8.3,1.5Hz), 7.67(1H,d,J=8.3Hz), 8.01(1H,d,J=1.5Hz).

MS (EI)  $m/z$ : 214( $\text{M}^+$ ,  $^{81}\text{Br}$ ), 212( $\text{M}^+$ ,  $^{79}\text{Br}$ ).

[Referential Example 215] 6-

Trimethylsilylethynylbenzo[b]thiophene

In tetrahydrofuran (15 ml) was dissolved 6-bromobenzo[b]thiophene (2.13 g), followed by the addition of triphenylphosphine (787 mg), triethylamine (40 ml), N,N-dimethylformamide (15 ml), trimethylsilylacetylene (1.47 g) and palladium acetate (225 mg). The resulting mixture was refluxed for 5 hours. After the reaction mixture was allowed to cool down, it was diluted with methylene chloride (150 ml). The diluted mixture was washed with water (twice) and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (only hexane), whereby the title compound (1.38 g) was obtained.

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.27 (9H, s), 7.30 (1H, d,  $J=5.7\text{Hz}$ ),  
7.44 (1H, dd,  $J=8.3, 1.0\text{Hz}$ ), 7.49 (1H, d,  $J=5.7\text{Hz}$ ),  
7.73 (1H, d,  $J=8.3\text{Hz}$ ), 8.00 (1H, s).  
MS (EI)  $m/z$ : 230  $\text{M}^+$ .

5 [Referential Example 216] 6-

Trimethylsilylethynylbenzo[b]thiophene-2-sulfonyl chloride

In anhydrous diethyl ether (10 ml) was dissolved 6-trimethylsilylethynylbenzo[b]thiophene (408 mg). After the resulting solution was cooled to  $-78^\circ\text{C}$ , tert-butyl lithium (a 1.54 mole pentane solution, 1.15 ml) was added dropwise.  
10 The reaction mixture was heated to  $0^\circ\text{C}$  over 30 minutes, followed by stirring for 1 hour. The reaction mixture was cooled again to  $-78^\circ\text{C}$  and then, a sulfur dioxide gas was introduced thereinto. After heating to room temperature  
15 over 1 hour, the mixture was stirred for 1 hour. The unreacted portion of sulfur dioxide gas which had been dissolved in the reaction mixture was volatilized sufficiently. The solvent was then distilled off under reduced pressure. Hexane (20 ml) was added to the residue.  
20 An insoluble precipitate was collected by filtration and washed with hexane. The precipitate was then dissolved in methylene chloride (10 ml). After cooling to  $0^\circ\text{C}$ , N-chlorosuccinic imide (248 mg) was added and the resulting mixture was stirred for 30 minutes and after heating to  
25 room temperature, stirred for further 1 hour.  
Water was added to the reaction mixture to separate

it into layers. The water layer was extracted with methylene chloride (5 times each with a 10 ml portion). The organic layers were combined, washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (498 mg) was obtained as a pale yellow solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.28 (9H, s), 7.58 (1H, dd,  $J=8.3, 1.5\text{Hz}$ ), 7.89 (1H, d,  $J=8.3\text{Hz}$ ), 8.02 (1H, s), 8.10 (1H, s).

MS (EI)  $m/z$ : 328  $\text{M}^+$ .

[Referential Example 217] 1-[(6-Trimethylsilylethynylbenzo[b]thien-2-yl)sulfonyl-3]-(N-methylcarbamoyl)piperazine

In methanol (15 ml) was dissolved 1,4-dibenzyl-2-(N-methylcarbamoyl)piperazine (437 mg). Palladium hydroxide (22 mg) and concentrated hydrochloric acid (0.22 ml) were then added to the resulting solution. A hydrogen gas was introduced (1 atmospheric pressure) into the resulting mixture, followed by stirring at room temperature for 1 hour. After the addition of triethylamine (0.9 ml), palladium was filtered off and the solvent was distilled off under reduced pressure. The residue was dissolved in methylene chloride. Triethylamine (0.5 ml) was added to the resulting mixture, followed by the addition of 6-trimethylsilylethynylbenzo[b]thiophene-2-sulfonyl chloride (399 mg) under ice cooling. After the temperature was

allowed to rise back to room temperature, stirring was conducted for 20 hours. The reaction mixture was washed (twice) with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methanol : methylene chloride = 1:19), whereby the title compound (462 mg) was obtained as a pale yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.28(9H,s), 1.52(1H,br s), 2.57-2.66(2H,m), 2.80, 2.79(total 3H,each s), 2.97(1H,dt,J=3.3,11.5Hz), 3.09(1H,dt,J=13.2,3.1Hz), 3.51(1H,dd,J=9.8,3.4Hz), 3.59(1H,dd,J=11.7,0.98Hz), 3.92(1H,dd,J=11.7,2.4Hz), 6.56-6.57(1H,m), 7.52(1H,dd,J=8.3,0.98Hz), 7.77(1H,s), 7.82(1H,d,J=8.3Hz), 7.97(1H,s).

MS (FAB) m/z: 436 (M+H)<sup>+</sup>.

[Referential Example 218] 1-(tert-Butoxycarbonyl)-4-[(5-bromopyridin-2-yl)carbonyl]piperazine

In the same manner as in Referential Example 3, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47(9H,s), 3.35-3.37(2H,m), 3.45-3.48(2H,m), 3.54-3.57(2H,m), 3.77-3.79(2H,m), 8.87(2H,s).

MS (FAB) m/z: 373 [(M+H)<sup>+</sup>, <sup>81</sup>Br], 371 [(M+H)<sup>+</sup>, <sup>79</sup>Br].



[Referential Example 219] 1-(tert-Butoxycarbonyl)-4-[[5-(4-pyridyl)pyrimidin-2-yl]carbonyl]piperazine

To a mixed solvent of dimethoxyethane (60 ml) and methanol (120 ml) were added 1-(tert-butoxycarbonyl)-4-[(5-bromopyrimidin-2-yl)carbonyl]piperazine (2.97 g), (pyridin-4-yl)boronic acid (1.48 g), cesium fluoride (4.25 g) and tetrakis(triphenylphosphine)palladium (924 mg). After purging with argon, the reaction mixture was refluxed for 19 hours. The solvent was then distilled off under reduced pressure. The residue was purified by moderate-pressure chromatography on a silica gel column (size D, methanol : methylene chloride = 1:9), whereby the title compound (1.31 g) was obtained as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.48 (9H, s), 3.40-3.44 (2H, m), 3.48-3.52 (2H, m), 3.59 (2H, t, J=5.4 Hz), 3.84 (2H, t, J=5.4 Hz), 7.54 (2H, dd, J=4.4, 2.0 Hz), 8.81 (2H, dd, J=4.4, 2.0 Hz), 9.07 (2H, s).

MS (FAB) m/z: 369 M<sup>+</sup>.

[Referential Example 220] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(methoxycarbonylmethyl)piperazine

To an ethanol solution (50 ml) of 1-(tert-butoxycarbonyl)-3-(3-methoxycarbonylmethyl)piperazine (5.03 g) was added a saturated solution of hydrochloride in ethanol (20 ml), followed by stirring for 30 minutes. After the solvent was distilled off under reduced pressure,

the residue was dissolved in methylene chloride to obtain a methylene chloride solution (200 ml). At room temperature, 5-chloro-1-phenylsulfonylindole-2-sulfonyl chloride (7.64 g) and triethylamine (9.5 ml) were added to the resulting solution, followed by stirring at room temperature for 4 hours. Distilled water and methylene chloride were added and the water layer was extracted three times. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue so obtained was subjected to chromatography on a silica gel column (methanol : methylene chloride = 1:50), whereby the title compound (4.97 g) was obtained as a colorless oil.

MS (FAB)  $m/z$ : 512  $[(M+H)^+, Cl^{35}]$ , 514  $[(M+H)^+, Cl^{37}]$ .

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 2.15-2.30 (1H, br), 2.34-2.49 (2H, m), 2.72-2.76 (1H, m), 2.90-3.22 (3H, m), 3.17-3.25 (1H, m), 3.67 (3H, s), 3.71-3.77 (2H, m), 7.39-7.47 (4H, m), 7.52-7.58 (2H, m), 8.02 (2H, d,  $J=7.8$  Hz), 8.23 (1H, d,  $J=9.3$  Hz).

[Referential Example 221] 1-(tert-Butoxycarbonyl)-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)piperazine

To an ethanol solution (250 ml) of 1-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(methoxycarbonylmethyl)piperazine (2.00 g) was added di-tert-butyl dicarbonate (3.91 g) at room temperature, followed by stirring for 17 hours. The reaction mixture

was concentrated under reduced pressure and diethyl ether was added to the concentrate. The crystals thus precipitated were collected by filtration, washed with diethyl ether and dried under reduced pressure, whereby the  
 5 title compound (2.01 g) was obtained as colorless crystals.  
 MS (FAB) m/z: 612 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 614 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45(9H,s), 2.45-2.54(1H,m), 2.74-  
 2.86(1H,m), 2.92-3.03(1H,m), 3.07-3.27(1H,m), 3.37(3H,s),  
 3.67-3.77(2H,m), 3.94-4.06(2H,m), 4.52-4.67(1H,m), 7.38-  
 10 7.49(4H,m), 7.57-7.60(2H,m), 8.03(2H,d,J=6.8Hz),  
 8.23(1H,d,J=9.3Hz).

[Referential Example 222] 1-(tert-Butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[[morpholin-4-yl]carbonyl]methyl]piperazine

15 To a 1,4-dioxane solution (100 ml) of 1-(tert-butoxycarbonyl)-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)piperazine (1.0 g) was added a 1N aqueous solution (4.9 ml) of sodium hydroxide at room temperature. The resulting mixture was  
 20 heated to 80°C and stirred for 6 hours. Under ice cooling, a saturated aqueous solution of ammonium chloride was added to neutralize the reaction mixture, followed by addition of distilled water. The water layer was extracted four times with methylene chloride. The organic layers were combined,  
 25 dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was

dissolved in methylene chloride to obtain a methylene chloride solution (150 ml). To the resulting solution were added 1-hydroxybenzotriazole (0.24 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.41 g), morpholine (0.16 g) and N-methylmorpholine (0.41 g), followed by stirring at room temperature for 12 hours. Distilled water was added to the reaction mixture. The water layer was extracted three times with methylene chloride. The organic layers were combined, washed four times with distilled water, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The resulting residue was subjected to chromatography on a silica gel column (methanol : methylene chloride 1:50), whereby the title compound (0.71 g) was obtained as a colorless solid.

$^1\text{H-NMR}$  (MHz,  $\text{CDCl}_3$ )  $\delta$ : 1.41(9H,s), 2.23-2.30(3H,m), 3.34-3.84(12H,m), 3.91-4.12(1H,m), 4.49-4.64(1H,m), 6.98(1H,s), 7.27-7.33(1H,m), 7.37(1H,d,J=8.8Hz), 7.66(1H,s).

MS (FAB) m/z: 527  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 529  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 223] 1-(tert-Butoxycarbonyl)-2-(carbamoylmethyl)-[(5-chloroindol-2-yl)sulfonyl]piperazine

To a 1,4-dioxane solution (100 ml) of 1-(tert-butoxycarbonyl)-4-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)piperazine (800 mg) was added a 1N aqueous solution of sodium hydroxide (3.9 ml) at room temperature. The resulting mixture was heated

to 80°C and stirred for 13 hours. Under ice cooling, a saturated aqueous solution of ammonium chloride was added to neutralize the reaction mixture, followed by the addition of distilled water and methylene chloride. The water layer was extracted 4 times with methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dried overnight under reduced pressure and then, an N,N'-dimethylformamide solution (50 ml) was obtained. At room temperature, di-tert-butyl dicarbonate (856 mg, 3.92 mmol), pyridine (259 mg) and ammonium bicarbonate (233 mg) were added to the resulting solution, followed by stirring at room temperature for 15 hours. The reaction mixture was distilled under reduced pressure to remove the solvent and the residue was dissolved in methylene chloride. Hexane and diethyl ether were added to solidify the resulting solution. The resulting solid was collected by filtration, washed with hexane and dried under reduced pressure, whereby the title compound (502 mg) was obtained as a colorless solid.

MS (FAB) m/z: 457 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 459 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

<sup>1</sup>H-NMR (MHz, CDCl<sub>3</sub>) δ: 0.88(1H,t,J=6.4Hz), 1.24-1.33(1H,m), 1.35-1.44(1H,m), 1.46(9H,s), 2.32-2.59(2H,m), 2.88-3.18(2H,m), 3.69-3.88(1H,m), 3.91-4.16(1H,m), 4.35-

4.82(1H,m), 5.91-6.60(1H,m), 6.97(1H,s), 7.26-7.29(1H,m),  
7.41(1H,d,J=8.8Hz), 7.66(1H,s).

[Referential Example 224] 1,4-Dibenzyl-2-ethenylpiperazine

After a solution of 1,4-dibenzyl-2-

5 (ethoxycarbonyl)piperazine (6.76 g) in methylene chloride  
(250 ml) was cooled to  $-78^{\circ}\text{C}$ , diisobutylaluminum hydride (a  
1.0 mol/l hexane solution, 39.90 ml) was added dropwise and  
the mixture was stirred at  $-78^{\circ}\text{C}$  for 2 hours. A saturated  
aqueous solution of ammonium chloride and methylene  
10 chloride were added to the reaction mixture. The water  
layer was extracted three times. The organic layers were  
combined, washed with distilled water and dried over  
anhydrous sodium sulfate. The residue obtained by  
distilling off the solvent under reduced pressure was  
15 provided for the subsequent reaction without purification.  
After cooling a tetrahydrofuran solution (150 ml) of  
methyltriphenylphosphonium iodide (8.07 g) to  $-78^{\circ}\text{C}$ , n-  
butyl lithium (a 1.52 mole hexane solution, 13.14 ml) was  
added dropwise and the mixture was stirred at  $-78^{\circ}\text{C}$  for 2  
20 hours. A solution of the residue, which residue had been  
obtained above, in tetrahydrofuran was then added. The  
reaction mixture was heated from  $-78^{\circ}\text{C}$  to  $0^{\circ}\text{C}$  while  
stirring for 4 hours and then, a saturated aqueous solution  
of ammonium chloride was added to terminate the reaction.  
25 Diethyl ether was added and the water layer was extracted  
three times. The organic layers were combined, washed with

saturated aqueous NaCl solution and dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure was subjected to chromatography on a silica gel column (methanol : methylene chloride = 1:50), whereby the title compound (3.22 g) was  
5 obtained as a pale yellow oil.

MS (EI) m/z: 292 M<sup>+</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.07-2.22(3H,m), 2.62-2.76(3H,m), 2.89-  
2.97(1H,m), 3.07(1H,d,J=13.2Hz), 3.43-3.56(2H,m),  
10 4.04(1H,d,J=13.2Hz), 5.15-5.32(2H,m), 5.77-5.88(1H,m),  
7.20-7.33(10H,m).

[Referential Example 225] 2-Ethylpiperazine hydrochloride

At room temperature, concentrated hydrochloric acid (6 ml) and palladium hydroxide (1.1 g) were added to  
15 solution (600 ml) of 1,4-dibenzyl-2-ethenylpiperazine (10.9 g) in ethanol, followed by stirring for 12 hours under a hydrogen gas stream of 1 atmospheric pressure. The catalyst was filtered off and the solvent was distilled off under reduced pressure. The resulting residue was  
20 solidified using methylene chloride - diethyl ether, followed by washing with diethyl ether. The resulting solid was dried under reduced pressure, whereby the title compound (6.516 g) was obtained as a brown solid.

MS (EI) m/z: 114 M<sup>+</sup>.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 0.95 (3H, t,  $J=7.8\text{Hz}$ ), 1.56-1.79 (2H, m),  
2.95-3.07 (1H, m), 3.15-3.54 (6H, m), 9.75 (4H, br).

[Referential Example 226] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(ethyl)piperazine

5 To a methylene chloride solution (700 ml) of 2-ethylpiperazine hydrochloride (5.00 g) were added 5-chloro-1-phenylsulfonylindol-2-sulfonyl chloride (7.14 g) and triethylamine (11.16 ml) and the resulting mixture was stirred at room temperature for 3 hours. Distilled water  
10 and methylene chloride were added and the water layer was extracted three times. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column  
15 (methanol : methylene chloride = 1:100), whereby the title compound (5.86 g) was obtained as a pale yellow oil.  
MS (EI)  $m/z$ : 468 ( $\text{M}^+$ ,  $\text{Cl}^{35}$ ), 470 ( $\text{M}^+$ ,  $\text{Cl}^{37}$ ).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.94 (3H, t,  $J=7.8\text{Hz}$ ), 1.33-1.46 (2H, m),  
2.53-2.62 (1H, m), 2.56-2.74 (1H, m), 2.87-3.07 (3H, m), 3.75-  
20 3.83 (2H, m), 7.38 (1H, s), 7.40-7.47 (3H, m), 7.53-7.57 (2H, m),  
8.00-8.05 (2H, m), 8.22 (1H, d,  $J=8.8\text{Hz}$ ).

[Referential Example 227] 1-[(5-Chloroindol-2-yl)sulfonyl]-3-(ethyl)piperazine

25 A 1N aqueous solution (16 ml) of sodium hydroxide was added to a 1,4-dioxane solution (200 ml) of 1-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(ethyl)piperazine



(3.78 g) and the resulting mixture was stirred at 80°C for 11.5 hours. A saturated aqueous solution of ammonium chloride was added to the reaction mixture. Distilled water and ethyl acetate were then added and the water layer was extracted three time. The organic layers were combined, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methanol : methylene chloride = 1:100), followed by crystallization from tetrahydrofuran - diethyl ether, whereby the title compound (2.54 g) was obtained as needle crystals.

<sup>1</sup>H-NMR (MHz, CDCl<sub>3</sub>) δ: 0.92(3H,t,J=7.8Hz), 1.25-1.42(2H,m), 2.09(1H,t,J=1.3Hz), 2.47(1H,dt,J=2.9,11.2Hz), 2.63-2.72(1H,m), 2.92(1H,dt,J=2.9,17.2Hz), 3.00-3.07(1H,m), 3.60-3.70(2H,m), 6.95(1H,s), 7.30(1H,dd,J=8.8,1.9Hz), 7.37(1H,d,J=8.8Hz), 7.67(1H,d,J=1.9Hz), 8.98(1H,br).

[Referential Example 228] 1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-ethylpiperazine

To an N,N-dimethylformamide solution (200 ml) of 1-[(5-chloroindol-2-yl)sulfonyl]-3-(ethyl)piperazine (2.54 g) were added benzotriazol-1-yl-oxo-tris-pyrrolidino-phosphonium hexafluorophosphate (4.84 g), 5-bromopyrimidine-2-carboxylic acid (1.83 g) and triethylamine (1.40 ml). The resulting mixture was stirred

at room temperature for 12 hours. Distilled water was added and the water layer was extracted three times with ethyl acetate. The organic layers were combined, washed three times with distilled water, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methanol : methylene chloride = 1:100), followed by crystallization from methylene chloride and washing with diethyl ether, whereby the title compound (3.18 g) was obtained as a colorless solid.

MS (FAB)  $m/z$ =512 ( $M^+$ ), 514 [ $(M+2)^+$ ], 516 [ $(M+4)^+$ ].

$^1\text{H-NMR}$  (MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.83(1.5H,t,J=7.3Hz),

1.03(1.5H,t,J=7.3Hz), 1.74-2.02(2H,m), 2.48-2.70(2H,m),

3.16-3.25(0.5H,m), 3.40-3.53(1H,m), 3.58(0.5H,m),

3.67(1H,t,J=11.0Hz), 3.79-3.92(1H,m), 4.65-4.70(0.5H,m),

4.78-4.85(0.5H,m), 6.94(1H,s), 7.33-7.39(1H,m), 7.68(1H,s),

8.79(1H,s), 8.83(2H,s).

[Referential Example 229] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-3-(ethyl)piperazine

To a methylene chloride solution (30 ml) of 2-ethylpiperazine hydrochloride (307 mg) was added (6-chlorobenzo[b]thien-2-yl)sulfonyl chloride (438 mg) and triethylamine (498 mg). The resulting mixture was stirred at room temperature for 26 hours. Distilled water and methylene chloride were added and the water layer was

extracted three times. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column

(methanol : methylene chloride = 1:20), whereby the title compound (255 mg) was obtained as a pale yellow oil.

MS (FAB)  $m/z$ : 345  $[(M+H)^+, Cl^{35}]$ , 347  $[(M+H)^+, Cl^{37}]$ .

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 0.95 (3H, t,  $J=7.8$ Hz), 1.24-1.46 (2H, m), 2.16 (1H, t,  $J=10.7$ Hz), 2.54 (1H, dt,  $J=2.9, 11.2$ Hz), 2.65-2.75 (1H, m), 2.95 (1H, dt,  $J=2.9, 11.2$ Hz), 3.04-3.10 (1H, m), 3.65-3.72 (2H, m), 7.43 (1H, dd,  $J=8.8, 2.0$ Hz), 7.75 (1H, s), 7.81 (1H, d,  $J=8.8$ Hz), 7.86 (1H, s).

[Referential Example 230] 1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-ethylpiperazine

Under an argon atmosphere,  $N,N$ -dimethylformamide (0.15 ml) was added to a methylene chloride solution (25 ml) of 5-bromopyrimidine-2-carboxylic acid (455 mg) was added and the resulting mixture was ice cooled. Oxalyl chloride (564 mg) was added and the resulting mixture was stirred for 30 minutes under ice cooling. The resulting solution, together with diisopropylethylamine (2.7 ml), was added to a methylene chloride solution (25 ml) of 1-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-3-ethylpiperazine (255 mg), followed by stirring at  $0^\circ C$  for 1 hour. The reaction mixture was added successively with a saturated aqueous

solution of ammonium chloride and distilled water. The water layer was extracted three times with methylene chloride. The organic layers were combined, washed three times with distilled water, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methanol : methylene chloride = 1:100), whereby the title compound (308 mg) was obtained as a pale yellow oil.

MS (FAB)  $m/z$ =529 ( $M^+$ ), 531 [ $(M+2)^+$ ], 533 [ $(M+4)^+$ ].

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.84 (1.5H, t,  $J=7.3\text{Hz}$ ), 1.05 (1.5H, t,  $J=7.3\text{Hz}$ ), 1.17-2.03 (0.5H, m), 1.76-2.04 (2H, m), 2.55-2.77 (2.5H, m), 3.17-3.28 (1H, m), 3.40-3.62 (1.5H, m), 3.67-3.77 (1H, m), 3.82-3.94 (1H, m), 4.65-4.70 (0.5H, m), 4.80-4.87 (0.5H, m), 7.45 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.75 (1H, s), 7.82 (1H, d,  $J=8.8\text{Hz}$ ), 7.87 (1H, br), 8.83 (2H, s).

[Referential Example 231] 1,4-Dibenzyl-2-(2-methyl-1-propenyl)piperazine

After cooling a methylene chloride solution (400 ml) of 1,4-dibenzyl-2-ethoxycarbonylpiperazine (19.57 g) to  $-78^\circ\text{C}$ , diisobutylaluminum hydride (a 0.95 mole hexane solution, 121.7 ml) was added dropwise. The resulting mixture was stirred at  $-78^\circ\text{C}$  for 2.5 hours. A saturated aqueous solution of ammonium chloride and methylene chloride were added and then, the water layer was extracted three times. The organic layers were combined, washed with

distilled water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was provided for the subsequent reaction without purification. After cooling a tetrahydrofuran solution (300 ml) of isopropyltriphenylphosphonium iodide (25.0 g) to  $-78^{\circ}\text{C}$ , n-butyl lithium (a 1.53 mole hexane solution, 37.8 ml) was added dropwise, followed by stirring at  $-78^{\circ}\text{C}$  for 30 minutes. A solution of the residue, which had been obtained above, in tetrahydrofuran was added dropwise to the reaction mixture. The resulting mixture was heated gradually from  $-78^{\circ}\text{C}$  and stirred overnight. A saturated aqueous solution of ammonium chloride was added to terminate the reaction. Ethyl acetate was added and the water layer was extracted three times. The organic layers were combined, washed with saturated aqueous NaCl solution and dried over anhydrous magnesium sulfate. The residue obtained by distilling off the solvent under reduced pressure The residue was subjected to chromatography on a silica gel column (ethyl acetate : hexane = 1:20), whereby the title compound (6.0 g) was obtained as a pale yellow oil.

MS (EI)  $m/z$ : 320  $\text{M}^+$ .

$^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, s), 0.91 (3H, s), 2.00 (1H, t,  $J=10.7\text{Hz}$ ), 2.04-2.21 (2H, m), 2.64-2.72 (3H, m), 3.00-3.18 (2H, m), 3.40-3.55 (2H, m), 4.06 (1H, d,  $J=13.7\text{Hz}$ ), 5.13 (1H, d,  $J=8.8\text{Hz}$ ), 7.16-7.45 (10H, m).

[Referential Example 232]

2-(2-Methylpropyl)piperazine hydrochloride

Concentrated hydrochloric acid (3 ml) and palladium hydroxide (683 mg) were added to an ethanol solution (300 ml) of 1,4-dibenzyl-2-(2-methyl-1-propenyl)piperazine (5.2 g), followed by stirring for 2 hours under a hydrogen gas stream of 1 atmospheric pressure. The catalyst was removed by filtration and the solvent was distilled off under reduced pressure. The residue was recrystallized from methylene chloride - hexane, followed by washing with diethyl ether and drying under reduced pressure, whereby the title compound (2.95 g) was obtained as a brown solid. MS (EI) m/z: 143 M<sup>+</sup>.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.86-1.30 (1H,m), 1.73 (3H,s), 1.76 (3H,s), 3.10-3.47 (7H,m), 4.36-4.45 (1H,m), 5.18 (1H,d, J=9.3Hz).

[Referential Example 233]

1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(2-methylpropyl)piperazine

To a methylene chloride solution (150 ml) of 2-(2-methylpropyl)piperazine hydrochloride (1.50 g) were added 5-chloro-1-phenylsulfonylindole-2-sulfonyl chloride (2.72 g) and triethylamine (2.91 ml). The resulting mixture was stirred at room temperature for 13 hours. Distilled water and methylene chloride were added and the water layer was extracted three times. The organic layers were combined,

washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methanol : methylene chloride = 1:20), whereby the title compound (2.69 g) was obtained as a brown oil.

MS (FAB) m/z: 496 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 498 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.89(1H,t,J=5.9Hz), 1.50-1.52(1H,m), 2.70-2.79(1H,m), 2.90-3.12(3H,m), 3.55-3.83(3H,m), 5.02(1H,d,J=8.3Hz), 7.35-7.48(4H,m), 7.51-7.58(2H,m), 8.02(2H,d,J=8.3Hz), 8.22(1H,d,J=8.8Hz).

[Referential Example 234]

1-[(5-Chloroindol-2-yl)sulfonyl]-3-(2-methylpropyl)piperazine

To a solution of 1-[(5-chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-(2-methylpropyl)piperazine (2.57 g) in a mixture of 1,4-dioxane and distilled water (100 - 10 ml) was added a 1N aqueous solution (10.4 ml) of sodium hydroxide. The resulting mixture was stirred at 80°C for 3 days. After saturated ammonium chloride was added to terminate the reaction, distilled water and ethyl acetate were added. The water layer was extracted three times. The organic layers were combined, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methanol : methylene

chloride = 1:50), whereby the title compound (0.93 g) was obtained as a brown oil.

MS (FAB)  $m/z$ : 356  $[(M+H)^+, Cl^{35}]$ , 358  $[(M+H)^+, Cl^{37}]$ .

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 0.78-1.30 (2H, m), 1.69 (3H, s), 1.70 (3H, s),  
 1.63-1.80 (1H, m), 2.39-2.55 (1H, m), 2.90-3.07 (2H, m), 3.48-  
 3.70 (3H, m), 4.90 (1H, d,  $J=8.3$  Hz), 6.92-6.99 (1H, m),  
 7.31 (1H, dd,  $J=8.8, 2.0$  Hz), 7.36 (1H, d,  $J=8.8$  Hz), 7.65-  
 7.69 (1H, m), 8.72 (1H, br).

[Referential Example 235] 1-[(5-Bromopyrimidin-2-yl)carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]-2-(2-methylpropyl)piperazine

To an N,N-dimethylformamide solution (60 ml) of 1-[(5-chloroindol-2-yl)sulfonyl]-3-(2-methylpropyl)piperazine (0.91 g) were added benzotriazol-1-yl-oxo-tris-pyrrolidino-phosphonium hexafluorophosphate (1.60 g), 5-bromopyrimidine-2-carboxylic acid (0.63 g) and triethylamine (0.39 g). The resulting mixture was stirred at room temperature for 14 hours. The solvent was then distilled off under reduced pressure. Distilled water was added to the residue and the water layer was extracted three times with methylene chloride. The organic layers were combined, washed three times with distilled water, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methanol : methylene chloride = 1 : 100), followed by



crystallization from ethanol - diethyl ether, whereby the title compound (0.47 g) was obtained as brown crystals.

MS (FAB)  $m/z$ =538 ( $M^+$ ), 540 [ $(M+2)^+$ ], 542 [ $(M+4)^+$ ].

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.70-1.28(2H,m), 1.60-1.75(1H,m),

5 1.79(3H,s), 1.82(3H,s), 2.53-2.90(2H,m), 3.34-3.48(0.5H,m),  
3.53-3.62(0.5H,m), 3.68-3.79(1H,m), 3.83-3.97(0.5H,m),  
4.54-4.66(0.5H,m), 5.64(1H,br), 6.95(1H,br),  
7.34(1H,dd,J=8.8,2.0Hz), 7.38(1H,d,J=8.8Hz), 7.69(1H,s),  
8.73(1H,s), 8.82(2H,br).

10 [Referential Example 236] 3-(5-Thiazolyl)pyridine

At room temperature,

tetrakis(triphenylphosphine)palladium (470 mg) was added to  
3-bromopyridine (805  $\mu\text{l}$ ) and a solution of (5-  
thiazolyl)trimethyltin (2.07 g) in benzene (80 ml),  
15 followed by heating under reflux overnight. After the  
reaction mixture was allowed to cool down to room  
temperature, it was washed with a saturated aqueous  
solution (100 ml) of sodium bicarbonate. The water layer  
was extracted with ethyl acetate (3 x 20 ml). The organic  
20 layers were combine, dried over anhydrous sodium sulfate  
and distilled under reduced pressure to remove the solvent.  
The residue was purified by chromatography on a silica gel  
column (hexane : ethyl acetate = 2:1), whereby the title  
compound (1.68 g, purity: 85%) was obtained as a colorless  
25 solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 7.37 (1H, dd, J=7.3, 4.9Hz),

7.88 (1H, dt, J=7.3, 1.5Hz), 8.14 (1H, s),

8.60 (1H, dd, J=4.9, 1.5Hz), 8.85 (1H, s), 8.86 (1H, d, J=1.5Hz).

[Referential Example 237] 1-(tert-Butoxycarbonyl)-4[5-(2-methylpyridin-4-yl)thiazol-2-yl]piperazine

At room temperature,

tetrakis(triphenylphosphine)palladium (470 mg) was added to a solution of 4-bromo-2-methylpyridine (1.65 g) and (5-thiazolyl)trimethyltin (1.56 g) in benzene (80 ml), followed by heating under reflux for 14 hours. After allowed to cool down to room temperature, the reaction mixture was washed with a saturated aqueous solution (100 ml) of sodium bicarbonate. The water layer was extracted with ethyl acetate (50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : ethyl acetate = 4:1 → 1:1), whereby 2-methyl-4-(5-thiazolyl)pyridine was obtained as a colorless solid. The resulting solid was dissolved in diethyl ether (30 ml) and tetrahydrofuran (30 ml), followed by the dropwise addition of n-butyl lithium (a 1.52N hexane solution, 4.35 ml) at -78°C. After stirring for 30 minutes, a carbon dioxide gas was blown into the reaction mixture. Thirty minutes later, the reaction mixture was heated gradually to room temperature. The reaction mixture

was concentrated, whereby the residue of lithium 5-(2-methylpyridin-4-yl)thiazole-2-carboxylate was obtained as a colorless solid. To a solution of the resulting residue in N,N-dimethylformamide (40 ml) were added 1-(tert-butoxycarbonyl)piperazine (1.30 g), 1-hydroxybenzotriazole monohydrate (945 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.34 g) at room temperature. After stirring for 3 days, ethyl acetate (200 ml) and water (800 ml) were added to the reaction mixture to separate it into layers. The water layer was extracted with ethyl acetate (2 x 100 ml). The organic layers were combined, washed with water (800 ml) and a saturated aqueous solution (200 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : acetone = 6:1), whereby the title compound (810 mg) was obtained as a colorless transparent viscous substance.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.49(9H,s), 2.63(3H,s), 3.57(4H,t,J=4.9Hz), 3.79(2H,br s), 4.43(2H,br s), 7.30(1H,d,J=4.9Hz), 7.35(1H,s), 8.14(1H,s), 8.56(1H,d,J=4.9Hz).

MS (FAB) m/z: 389 (M+H)<sup>+</sup>, 333 (M+H-isobutene)<sup>+</sup>, 289 (M+H-Boc)<sup>+</sup>.

[Referential Example 238] 1-(tert-Butoxycarbonyl)-4-[5-(pyridin-4-yl)thiazol-2-yl]piperazine

Diethyl ether and a saturated aqueous solution of sodium bicarbonate were added to 4-bromopyridine hydrochloride (3.76 g). The organic layer thus separated was dried over anhydrous sodium sulfate and concentrated under reduced pressure, whereby a diethyl ether solution of 4-bromopyridine was obtained. To the resulting solution were added (5-thiazolyl)trimethyltin (4.00 g), benzene (150 ml) and tetrakis(triphenylphosphine)palladium (950 mg), followed by heating under reflux for 12 hours. After allowed to cool down to room temperature, the reaction mixture was added with a saturated aqueous solution (100 ml) of sodium bicarbonate and ethyl acetate (50 ml). The water layer thus separated was extracted with ethyl acetate (2 x 50 ml) and methylene chloride (2 x 50 ml). The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : ethyl acetate = 5:1  $\rightarrow$  2:1), whereby 4-(5-thiazolyl)pyridine was obtained as a colorless, transparent oil. The resulting oil was dissolved in diethyl ether (80 ml), followed by the dropwise addition of n-butyl lithium (a 1.52N hexane solution, 11.5 ml) at  $-78^{\circ}\text{C}$ . After stirring for 30 minutes, a carbon dioxide gas was blown

into the reaction mixture. Ten minutes later, the temperature was increased gradually to room temperature. The reaction mixture was concentrated, whereby the residue of lithium 5-(pyridin-4-yl)thiazole-2-carboxylate was obtained as a colorless solid. To a solution of the resulting residue in N,N-dimethylformamide (50 ml) were added 1-(tert-butoxycarbonyl)piperazine (3.30 g), 1-hydroxybenzotriazole monohydrate (2.40 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.40 g) at room temperature. The resulting mixture was stirred for 3 days. Ethyl acetate (200 ml) and water (2000 ml) were added to the reaction mixture. The water layer thus separated was extracted with ethyl acetate (2 x 200 ml). The organic layers were combined, washed with water (1000 ml) and a saturated aqueous solution (400 ml) of sodium bicarbonate, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was reprecipitated in a methylene chloride - hexane system, whereby the title compound (3.00 g) was obtained as pale brown powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49(9H,s), 3.57(4H,t,J=5.6Hz), 3.79(2H,br s), 4.43(2H,br s), 7.49(2H,d,J=5.9Hz), 8.17(1H,s), 8.69(2H,d,J=5.9Hz).

MS (FAB)  $m/z$ : 375 ( $\text{M}+\text{H}$ ) $^+$ , 319 ( $\text{M}+\text{H}$ -isobutene) $^+$ , 275 ( $\text{M}+\text{H}$ -Boc) $^+$ .

[Referential Example 239] 5-(Pyridin-4-yl)thiazole

In a 3M aqueous solution of potassium carbonate, 4-bromopyridine hydrochloride (389 mg) was suspended, followed by extraction with diethyl ether. The organic layer thus extracted with dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in benzene (20 ml), followed by the addition of 5-trimethylstannylthiazole (496 mg) (Synthesis, 198, 757) and tetrakis(triphenylphosphine)palladium (116 mg). In an argon gas stream, the resulting mixture was heated under reflux for 48 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby the title compound (293 mg) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.47 (2H, dd,  $J=4.9, 2.0\text{Hz}$ ), 8.27 (1H, s), 8.65 (2H, dd,  $J=4.9, 2.0\text{Hz}$ ), 8.89 (1H, s).

MS (FAB)  $m/z$ : 163 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 240] Lithium 5-(pyridin-4-yl)thiazole-2-carboxylate

In diethyl ether (20 ml) was dissolved 5-(pyridin-4-yl)thiazole (290 mg), followed by the dropwise addition of an n-hexane solution (1.54M, 1.20 ml) of n-butyl lithium at  $-78^\circ\text{C}$ . The resulting mixture was stirred for 10 minutes. After a carbon dioxide gas was blown into the reaction mixture at  $-78^\circ\text{C}$  for 15 minutes, the reaction mixture was

heated to room temperature. The reaction mixture was concentrated under reduced pressure, whereby the title compound (409 mg) was obtained as a pale brown foam.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 7.66(2H,d,J=5.4Hz), 8.37(1H,s),

5 8.59(2H,d,J=5.4Hz), .

MS (FD)  $m/z$ : 213 ( $\text{M+Li+H}$ ) $^+$ .

[Referential Example 241] 5-(Pyridin-2-yl)thiazole

In the same manner as in Referential Example 239, the title compound was obtained.

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.22(1H,t,J=5.9Hz), 7.67-7.78(3H,m),

8.34(1H,s), 8.60(1H,d,J=4.9Hz), 8.84(1H,s).

MS (FAB)  $m/z$ : 163 ( $\text{M+H}$ ) $^+$ .

[Referential Example 242] Lithium 5-(pyridin-2-yl)thiazole-2-carboxylate

15 In the same manner as in Referential Example 240, the title compound was synthesized.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 7.31(1H,m), 7.85(1H,t,J=7.8Hz),

7.94(1H,d,J=7.8Hz), 8.36(1H,s), 8.56(1H,d,J=4.4Hz).

[Referential Example 243] (5-tert-Butyldimethylsilyloxy-4-

20 oxo-4H-pyran-2-yl)methyl chloride

Kojic acid (5.00 g) was dissolved in methylene chloride (300 ml). To the resulting solution were added N,N-dimethylformamide (0.03 ml) and thionyl chloride (3.08 ml) under ice cooling, followed by stirring overnight at

25 room temperature. The reaction mixture was concentrated

under reduced pressure. The residue was dissolved in tetrahydrofuran (600 ml). To the resulting solution were added triethylamine (19.51 ml), N,N-dimethylaminopyridine (0.20 g) and tert-butyldimethylsilyl chloride (7.95 g), followed by stirring at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. Methylene chloride was added to the residue. The resulting mixture was washed successively with a 0.3N aqueous solution of hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 8:1), whereby the title compound (6.10 g) was obtained as a pale brown oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.23(6H,s), 0.95(9H,s), 4.30(2H,s), 6.43(1H,s), 7.67(1H,s).

MS (FAB)  $m/z$ : 275 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 244] [(5-tert-Butyldimethylsilyloxy-4-oxo-4H-pyran-2-yl)methyl]amine

In N,N-dimethylformamide (20 ml) was dissolved (5-tert-butyldimethylsilyloxy-4-oxo-4H-pyran-2-yl)methyl chloride (2.00 g). Sodium azide (1.00 g) was added to the resulting solution and the resulting mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was



added to the residue, followed by washing once with water and then once with saturated aqueous NaCl solution. The organic layer thus extracted was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The resulting residue was dissolved in methanol (100 ml), followed by the addition of 10% palladium-carbon (50% wet w/w, 800 mg). The resulting mixture was stirred overnight under a hydrogen gas stream of normal pressure. The reaction mixture was subjected to Celite filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 100:3), whereby the title compound (290 mg) was obtained as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.23(6H,s), 0.95(9H,s), 3.68(2H,s), 6.35(1H,s), 7.64(1H,s).

MS (FAB) m/z: 256 (M+H)<sup>+</sup>.

[Referential Example 245] 1-(tert-Butoxycarbonyl)-2-[N-[(5-tert-butyldimethylsilyloxy-4-oxo-4H-pyran-2-yl)methyl]carbamoyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 5, the title compound was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 0.15(6H,s), 0.91(9H,s), 1.30(9H,br s), 2.34-2.44(1H,m), 2.56-2.71(1H,m), 3.19-3.46(1H,m), 3.55-3.68(1H,m), 3.77-3.94(1H,m), 4.03-4.32(3H,m), 4.50-

4.69(1H,m), 6.22(1H,br s), 7.00(1H,s),  
 7.32(1H,dd,J=8.8,2.0Hz), 7.49(1H,d,J=8.8Hz),  
 7.79(1H,d,J=2.0Hz), 8.12(1H,s), 8.66(1H,br s), 12.43(1H,s).  
 MS (FAB) m/z: 681 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 683 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

5 [Referential Example 246] 1-(tert-Butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-[N-[(5-hydroxy-4-oxo-4H-pyran-2-yl)methyl]carbamoyl]piperazine

In tetrahydrofuran (10 ml) was dissolved 1-(tert-butoxycarbonyl)-2-[N-[(5-tert-butyldimethylsilylox-4-oxo-4H-pyran-2-yl)methyl]carbonyl]-4-[(5-chloroindol-2-yl)sulfonyl]piperazine (570 mg), followed by the addition of a 1.0M tetrahydrofuran solution (8.37 ml) of tetrabutylammonium fluoride. The resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 100:3), whereby the title compound (475 mg) was obtained as a pale yellow foam.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.31(9H,br s), 2.30-2.86(2H,m), 3.12-3.19(1H,m), 3.52-3.68(1H,m), 3.80-3.94(1H,m), 4.00-4.30(3H,m), 4.51-4.69(1H,m), 6.23(1H,br s), 7.00(1H,s), 7.32(1H,dd,J=8.8,2.0Hz), 7.49(1H,d,J=8.8Hz), 7.79(1H,d,J=2.0Hz), 8.01(1H,s), 8.68(1H,br s), 12.44(1H,br s).

25 MS (FAB) m/z: 567 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 569 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 247] 2-[N-[(5-Acetoxy-4-oxo-4H-pyran-2-yl)methyl]carbamoyl]-1-(tert-butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]piperazine

In acetonitrile (10 ml) was dissolved 1-(tert-butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-[N-[(5-hydroxy-4-oxo-4H-pyran-2-yl)methyl]carbamoyl]piperazine (411 mg), followed by the addition of acetic anhydride (0.075 ml) and triethylamine (0.11 ml). The resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was concentrated under reduced pressure. Methylene chloride was added to the residue. The resulting mixture was washed successively with 0.2N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and saturated aqueous NaCl solution. The organic layer was then dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (methylene chloride : methanol = 50:5), whereby the title compound (256 mg) was obtained as a colorless foam.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.32(9H, br s), 2.25(3H, s), 2.31-2.70(2H, m), 3.00(1H, br s), 3.63(1H, br s), 3.86(1H, br s), 4.01-4.33(3H, m), 4.52-4.70(1H, m), 6.30(1H, br s), 7.01(1H, s), 7.32(1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.49(1H, d,  $J=8.8\text{Hz}$ ), 7.79(1H, d,  $J=2.0\text{Hz}$ ), 8.45(1H, s), 8.72(1H, br s), 12.44(1H, s).  
 MS (FAB)  $m/z$ : 609  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 611  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 248]

3-[N-[(5-Acetoxy-4-oxo-4H-pyran-2-yl)methyl]carbamoyl]-1-  
[(5-chloroindol-2-yl)sulfonyl]piperazine trifluoroacetate

In methylene chloride (5 ml), 2-[N-[(5-acetoxy-4-oxo-  
5 4H-pyran-2-yl)methyl]carbamoyl]-1-(tert-butoxycarbonyl)-4-  
[(5-chloroindol-2-yl)sulfonyl]piperazine was treated with  
trifluoroacetic acid (5 ml), followed by concentration to  
dryness under reduced pressure, whereby the title compound  
(224 mg) was obtained.

10  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.26(3H,s), 2.57-2.72(2H,m), 3.14-  
3.23(1H,m), 3.39(1H,d,J=11.7Hz), 3.65(1H,d,J=11.7Hz), 4.03-  
4.09(1H,m), 4.17-4.26(1H,m), 4.34-4.42(1H,m), 6.46(1H,s),  
7.12(1H,s), 7.36(1H,dd,J=8.8,2.0Hz), 7.52(1H,d,J=8.8Hz),  
7.82(1H,d,J=2.0Hz), 8.50(1H,s), 9.42(1H,br s), 12.57(1H,s).

15 MS (FAB)  $m/z$ : 509  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 511  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 249] N-[[1-[(5-Chloroindol-2-  
yl)sulfonyl]piperazin-3-yl]acetyl]methanesulfonamide  
trifluoroacetate

In tetrahydrofuran (5 ml) was dissolved 1-(tert-  
20 butoxycarbonyl)-2-[(carboxy)methyl]-4-[(5-chloroindol-2-  
yl)sulfonyl]piperazine (772 mg), followed by the addition  
of carbonyldiimidazole (820 mg). The resulting mixture was  
heated under reflux for 1 hour. After cooling to room  
temperature, the reaction mixture was added with  
25 methanesulfonamide (322 mg) and 1,8-diazabicyclo[5.4.0]-7-  
undecene (0.50 ml), followed by stirring overnight. The

reaction mixture was concentrated under reduced pressure. To the residue was added a 1N aqueous solution of hydrochloric acid. After removal of the supernatant, the precipitate was washed with water and dried, whereby a colorless foam was obtained. The substance was dissolved in methylene chloride (10 ml), followed by the addition of trifluoroacetic acid (10 ml). The resulting mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure. Diethyl ether was added to the residue and the precipitate thus obtained was collected by filtration, whereby the title compound (863 mg) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.53-2.74 (3H,m), 3.25 (3H,s), 3.43-3.50 (2H,m), 3.61-3.80 (4H,m), 7.10 (1H,s), 7.34 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.50 (1H,d,  $J=8.8\text{Hz}$ ), 7.80 (1H,d,  $J=2.0\text{Hz}$ ), 12.58 (1H,s).

MS (FAB)  $m/z$ : 435  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 437  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 250] 1-(tert-Butoxycarbonyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonyl)piperazine

In methylene chloride (200 ml) was dissolved 2-ethoxycarbonylpiperazine acetate (2.08 g), followed by the addition of triethylamine (3.63 ml). The resulting mixture was stirred overnight at room temperature. To the reaction mixture, a methylene chloride solution (20 ml) of 6-chlorobenzo[b]thiophene-2-sulfonyl chloride (2.00 g) was

slowly added dropwise over 2 hours. After stirring at room temperature for 30 minutes, di-tert-butyl dicarbonate (3.27 g) was added and the resulting mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed successively with 1N hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and saturated aqueous NaCl solution. The organic layer thus extracted was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 8:1), whereby the title compound (2.26 g) was obtained as a pale yellow foam.

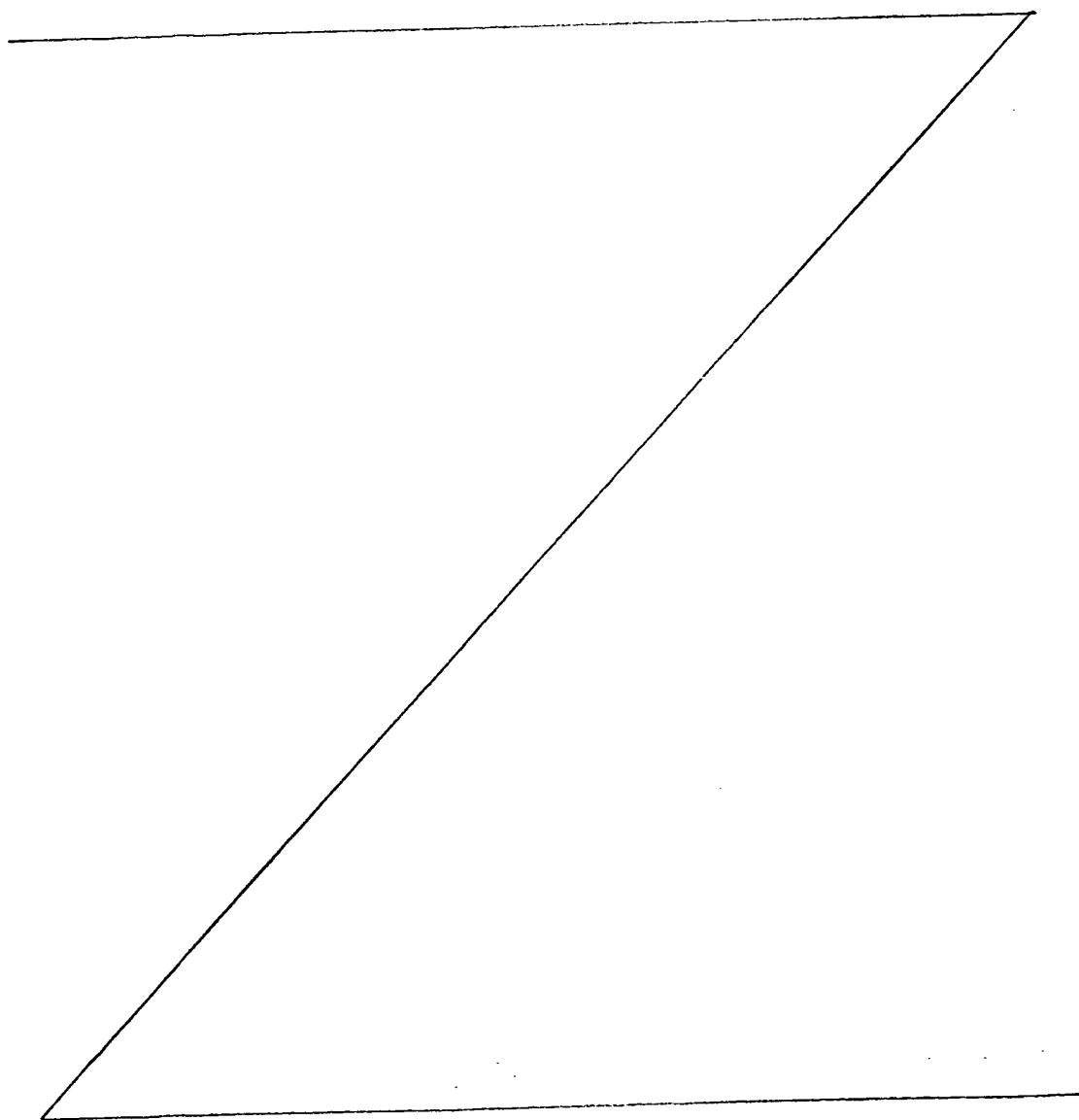
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.30 (3H, t, J=7.3Hz), 1.36-1.49 (9H, m), 2.52 (1H, td, J=11.7, 3.4Hz), 2.66-2.77 (1H, m), 3.20-3.42 (1H, m), 3.68-3.82 (1H, m), 3.87-4.08 (1H, m), 4.17-4.40 (1H, m), 4.68 (1/2H, br s), 4.87 (1/2H, br s), 7.43 (1H, dd, J=8.3, 2.0Hz), 7.77 (1H, s), 7.82 (1H, d, J=8.3Hz), 7.86 (1H, d, J=2.0Hz).

MS (FAB) m/z: 489 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 491 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 251] 1-(tert-Butoxycarbonyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine-2-carboxylic acid

In tetrahydrofuran (10 ml) was dissolved 1-(tert-butoxycarbonyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-(ethoxycarbonyl)piperazine (2.25 g), followed by the

addition of ethanol (20 ml) and a 3N aqueous solution (3 ml) of sodium hydroxide. The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was  
5 adjusted to have pH of 1 to 2 by the addition of a 1N aqueous solution of hydrochloric acid. Ethyl acetate was



then added and the organic layer was collected. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The solid thus precipitated was collected by filtration, whereby the title compound (2.17 g) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.44 (9H, s), 2.54 (1H, dt,  $J=11.7, 3.4\text{Hz}$ ), 2.69-2.79 (1H, m), 3.20-3.44 (1H, m), 3.70-3.84 (1H, m), 3.89-4.12 (1H, m), 4.30-4.41 (1H, m), 4.78 (1/2H, br s), 4.98 (1/2H, br s), 7.45 (1H, dd,  $J=8.3, 2.0\text{Hz}$ ), 7.79 (1H, s), 7.83 (1H, d,  $J=8.3\text{Hz}$ ), 7.88 (1H, d,  $J=2.0\text{Hz}$ ).

MS (FAB)  $m/z$ : 461  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 463  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 252] 1-[(6-Chlorobenzo[b]thine-2-yl)sulfonyl]-3-[(N-methyl)carbamoyl]piperazine hydrochloride

In N,N-dimethylformamide (50 ml) were dissolved 1-(tert-butoxycarbonyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine-2-carboxylic acid (691 mg), N-methylamine hydrochloride (111 mg), 1-hydroxybenzotriazole monohydrate (230 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (345 mg). Triethylamine (0.23 ml) was added to the resulting solution, followed by stirring overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue, followed by washing with water. The organic layer was dried over anhydrous sodium



sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 100:1), whereby a pale yellow foam was obtained. The resulting foam was dissolved in a saturated hydrochloric acid/ethanol solution (10 ml) and the resulting solution was concentrated under reduced pressure. The solid thus precipitated was collected by filtration while being washed with ethyl acetate, whereby the title compound (468 mg) was obtained as a colorless solid.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.67 (3H, d,  $J=4.4\text{Hz}$ ), 2.77 (1H, t,  $J=11.2\text{Hz}$ ), 2.87 (1H, t,  $J=11.2\text{Hz}$ ), 3.15-3.25 (1H, m), 3.32-3.40 (1H, m), 3.70 (1H, d,  $J=12.7\text{Hz}$ ), 3.98-4.03 (1H, m), 4.07-4.15 (1H, m), 7.62 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 8.11 (1H, d,  $J=8.8\text{Hz}$ ), 8.22 (1H, s), 8.40 (1H, d,  $J=2.0\text{Hz}$ ), 8.80 (1H, d,  $J=4.4\text{Hz}$ ).

MS (FAB)  $m/z$ : 374  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 376  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 253] Ethyl (piperazin-1-yl)acetate hydrochloride

In  $\text{N,N}$ -dimethylformamide (50 ml) was dissolved 1-(tert-butoxycarbonyl)piperazine (942 mg). After the addition of triethylamine (1.40 ml), ethyl bromoacetate (1.13 ml) was added, followed by stirring overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the mixture was washed with water. The organic layer

was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby a colorless foam was obtained. The resulting substance was dissolved in a saturated hydrochloric acid - ethanol solution (10 ml) and the resulting solution was concentrated under reduced pressure. The solid thus precipitated was collected by filtration while being washed with ethyl acetate, whereby the title compound (841 mg) was obtained as a colorless solid.

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.24(3H,t,J=7.3Hz), 3.36(8H,br s), 4.08(2H,br s), 4.18(2H,q,J=7.3Hz), 9.73(2H,br s).  
MS (FAB) m/z: 173 (M+H) $^+$ .

In the same manner as in Referential Example 252, the compounds shown in Referential Examples 254 to 255 were synthesized.

[Referential Example 254] Ethyl [4-[[1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]piperazin-1-yl]acetate hydrochloride

$^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$ : 1.26(3H,t,J=7.3Hz), 2.51-2.78(1H,m), 2.90-4.32(17H,m), 4.79(1H,br s), 7.76(1H,dd,J=8.8,2.0Hz), 7.90(1H,d,J=8.8Hz), 8.22(1H,d,J=8.8Hz), 8.29(1H,s), 8.32(1H,d,J=8.8Hz), 8.63(1H,s), 8.90(1H,br s).  
MS (FAB) m/z: 509 [(M+H) $^+$ , Cl $^{35}$ ], 511 [(M+H) $^+$ , Cl $^{37}$ ].

[Referential Example 255] 5-[[[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]carbonyl]amino]methyl]tetrazole trifluoroacetate

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.53-2.68 (2H,m), 3.15-3.23 (1H,m), 3.30-3.37 (1H,m), 3.68-3.76 (1H,m), 4.12-4.20 (2H,m), 4.65-4.68 (2H,m), 7.76 (1H,dd,J=8.8,2.0Hz), 7.86 (1H,dd,J=8.8,2.0Hz), 8.26 (1H,d,J=8.8Hz), 8.30-8.34 (2H,m), 8.56 (1H,s), 9.51-9.59 (1H,m).

MS (FAB) m/z: 435 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 437 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

10 [Referential Example 256] [1-(tert-Butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-2-yl]acetic hydrazinamide

In tetrahydrofuran (20 ml) was dissolved 1-[1-(tert-butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-2-yl]acetic acid (1.11 g). To the  
15 resulting solution, N-methylmorpholine (0.26 ml) and isobutyl chloroformate (0.31 ml) were successively added dropwise at -20°C. After stirring at -20°C for 10 minutes, hydrazine hydrate (690 ml) was added. The reaction mixture  
20 was concentrated under reduced pressure. The residue was dissolved in ethyl acetate. The resulting solution was washed with a 1N aqueous solution of hydrochloric acid, saturated sodium bicarbonate and saturated aqueous NaCl solution, each once. The organic layer was dried over  
25 anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column [methylene chloride : methanol = 100:0 to 100:1], whereby the title compound (513 mg) was obtained as a colorless foam.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.31(9H,s), 2.14-2.38(3H,m), 3.00-

5 3.12(1H,m), 3.57-3.68(2H,m), 3.83-3.90(1H,m), 4.16(2H,br s), 4.51(1H,br s), 7.70(1H,dd,J=8.8,2.0Hz), 7.78(1H,d,J=8.8Hz), 8.15(1H,d,J=8.8Hz), 8.23(1H,s), 8.25(1H,d,J=8.8Hz), 8.47(1H,s), 9.08(1H,s).

MS (FAB)  $m/z$ : 483  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 485  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 [Referential Example 257] 2-[[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]methyl]-4,5-dihydro-5-oxo-1,3,4-oxadiazole trifluoroacetate

In tetrahydrofuran (2 ml) was dissolved [1-(tert-butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-2-yl]acetic hydrazinamide (505 mg),  
 15 followed by the addition of carbonyl diimidazole (102 mg) and triethylamine (0.14 ml). The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. Methylene  
 20 chloride was added to the residue. The resulting mixture was washed with a 1N aqueous solution of hydrochloric acid, water and saturated aqueous NaCl solution, each once. The organic layer so extracted was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the  
 25 solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 100:0 to

100:1), whereby a colorless foam was obtained. The resulting substance was dissolved in methylene chloride (2 ml), followed by the addition of trifluoroacetic acid (5 ml). After stirring at room temperature for 1 minute, the reaction mixture was concentrated under reduced pressure. The residue was washed with diethyl ether. The precipitate thus obtained was collected by filtration, whereby the title compound (412 mg) was obtained as a colorless foam.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 2.60-2.79 (2H, m),  
 2.85 (1H, dd,  $J=16.1, 6.8\text{Hz}$ ), 3.03 (1H, dd,  $J=16.1, 6.8\text{Hz}$ ),  
 3.20 (1H, d,  $J=10.2\text{Hz}$ ), 3.43 (1H, d,  $J=12.7\text{Hz}$ ),  
 3.71 (1H, d,  $J=11.2\text{Hz}$ ), 3.90 (1H, d,  $J=11.2\text{Hz}$ ),  
 7.74 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.86 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ),  
 8.21 (1H, d,  $J=8.8\text{Hz}$ ), 8.27 (1H, s), 8.28 (1H, d,  $J=8.8\text{Hz}$ ),  
 8.55 (1H, s), 12.30 (1H, s).

MS (FAB)  $m/z$ : 409  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 411  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 258] 1-(tert-Butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(2-hydroxyethyl)piperazine

In tetrahydrofuran (100 ml) was dissolved 1-[1-(tert-butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazin-2-yl]acetic acid (2.00 g). The resulting solution was successively added dropwise with N-methylmorpholine (0.51 ml) and isobutyl chloroformate (0.64 ml) at  $-20^\circ\text{C}$ . After stirring at  $-20^\circ\text{C}$  for 10 minutes, sodium borohydride (483 mg) and methanol (20 ml) were added

successively to the reaction mixture. The resulting mixture was stirred for 10 minutes. After concentration under reduced pressure, the residue was dissolved in ethyl acetate. The resulting solution was washed with a 1N aqueous solution of hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and saturated aqueous NaCl solution, each once. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 100:0 to 100:3), whereby the title compound (1.75 g) was obtained as a colorless foam.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40(9H,s), 1.72-1.85(1H,m), 2.08-2.18(1H,m), 2.33(1H,dt,J=11.7,3.4Hz), 2.50-2.59(1H,m), 3.07(1H,dt,J=3.4,12.7Hz), 3.25-3.42(1H,m), 3.60-3.78(3H,m), 3.90-3.98(1H,m), 4.37-4.44(1H,m), 7.58(1H,dd,J=8.8,2.0Hz), 7.74(1H,dd,J=8.8,2.0Hz), 7.88-7.95(3H,m), 8.29(1H,s).

MS (FAB)  $m/z$ : 455  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 457  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 259] 2-(2-Bromoethyl)-1-(tert-butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In methylene chloride (50 ml) was dissolved 1-(tert-butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(2-hydroxyethyl)piperazine (1.00 g), followed by the addition of carbon tetrabromide (1.46 g) and triphenylphosphine (1.15 g). The resulting mixture was stirred at room

temperature for 30 minutes. After the addition of a saturated aqueous solution of sodium sulfite, the organic layer was collected from the mixture. The organic layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column [hexane : ethyl acetate = 10:1 to 6:1], whereby the title compound (990 mg) was obtained as a colorless foam.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.41 (9H, s), 2.20-2.41 (3H, m), 2.44 (1H, dd,  $J=12.2, 3.9\text{Hz}$ ), 3.04-3.15 (1H, m), 3.43 (1H, br s), 3.68 (1H, d,  $J=12.2\text{Hz}$ ), 3.77 (1H, d,  $J=10.7\text{Hz}$ ), 3.95-4.15 (1H, m), 4.46 (1H, br s), 7.58 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.74 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.87-7.94 (3H, m), 8.29 (1H, s).  
MS (FAB)  $m/z$ : 518  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 520  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 260] 1-(tert-Butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(2-cyanoethyl)piperazine

In  $\text{N,N}$ -dimethylformamide (20 ml) was dissolved 2-(2-bromoethyl)-1-(tert-butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (980 mg), followed by the addition of sodium cyanide (102 mg). The resulting mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed with water and saturated aqueous NaCl solution, each once. The organic layer thus extracted was dried over anhydrous sodium sulfate and distilled under reduced

pressure to remove the solvent, whereby the title compound (842 mg) was obtained as a colorless foam.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.41(9H,s), 1.92-2.03(1H,m), 2.21-2.44(4H,m), 2.48(1H,dd,J=11.7,3.9Hz), 3.13(1H,br s), 3.68(1H,d,J=11.7Hz), 3.77(1H,d,J=11.7Hz), 4.09(1H,br s), 4.38(1H,br s), 7.58(1H,dd,J=8.8,2.0Hz), 7.73(1H,dd,J=8.8,2.0Hz), 7.88-7.95(3H,m), 8.29(1H,s).  
MS (FAB)  $m/z$ : 464  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 466  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 261] 5-[2-[1-[(6-Chloronaphthalen-2-yl)sulfonyl]piperazin-3-yl]ethyl]tetrazole

In N,N-dimethylformamide (1.5 ml) was dissolved 1-(tert-butoxycarbonyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(2-cyanoethyl)piperazine (529 mg), followed by the addition of ammonium chloride (588 mg) and sodium azide (741 mg). The resulting mixture was stirred under heating at 100°C. The reaction mixture was concentrated under reduced pressure. Ethyl acetate was added to the residue and the resulting mixture was washed with water and saturated aqueous NaCl solution, each once. The organic layer thus extracted was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 50:1), whereby a colorless foam was obtained. The resulting substance was dissolved in methylene chloride (5 ml), followed by the addition of trifluoroacetic acid (5 ml).



The mixture was stirred at room temperature for 1 minutes.

The reaction mixture was concentrated under reduced pressure. The precipitate thus obtained was washed with diethyl ether and collected by filtration, whereby the

5 title compound (141 mg) was obtained as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.95-2.08 (2H,m), 2.45-2.70 (2H,m), 2.98-3.22 (3H,m), 3.35-3.51 (2H,m), 3.62-3.88 (2H,m), 7.75 (1H,d,J=8.8Hz), 7.88 (1H,d,J=8.8Hz), 8.20 (1H,d,J=8.8Hz), 8.27 (1H,s), 8.29 (1H,d,J=8.8Hz), 8.56 (1H,s).

10 MS (FAB) m/z: 407 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 409 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

In the same manner as in Example A-4, the compounds shown in Referential Examples 262 and 263 were obtained.

[Referential Example 262] 1-(tert-Butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-[(N-methylcabamoyl)methyl]piperazine

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.40 (9H,s), 2.34-2.45 (1H,br), 2.50-2.63 (1H,br), 2.63-2.80 (2H,br), 2.83 (3H,d,J=4.6Hz), 2.98-3.10 (1H,m), 3.65-4.15 (3H,br), 4.62 (1H,br s), 6.05-6.25 (1H,br), 6.97 (1H,d,J=1.7Hz), 7.29 (1H,dd,J=8.8,1.7Hz), 7.40 (1H,d,J=8.8Hz), 7.66 (1H,d,J=1.7Hz).

20 MS (FAB) m/z: 471 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 473 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 263] 1-(tert-Butoxycarbonyl)-4-[(5-chloroindol-2-yl)sulfonyl]-2-[[N-(tetrahydrofurfuryl)carbamoyl)methyl]piperazine

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.42(9H,s), 1.50-1.70(1H,m), 1.85-2.10(3H,m), 2.25-2.35(1H,br), 2.50-2.85(3H,br), 2.89-3.20(2H,m), 3.25-3.50(1H,br), 3.55-4.17(6H,m), 4.57(1H,br s), 6.29(1H,br s), 6.90-6.97(1H,m), 7.21-7.38(2H,m), 7.60-7.68(1H,m).

MS (FAB) m/z: 541 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 543 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 264] 1,4-Dibenzyl-2-(2-formylmethyl)piperazine

In methylene chloride (30 mL) was dissolved 1,4-dibenzyl-2-(2-hydroxyethyl)piperazine (620 mg), followed by the addition of 4-methylmorpholine N-oxide (281 mg) and tetrapropylammonium perruthenate (141 mg) under ice cooling. Ten minutes later, the resulting mixture was allowed to rise back to room temperature, followed by stirring. After 18 hours, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column (ethyl acetate : hexane = 1:1), whereby the title compound (360 mg) was obtained as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.33-2.82(8H,m), 3.13(1H,brs), 3.34(1H,d,J=13.2Hz), 3.48(2H,ABq,J=13.2Hz), 3.81(1H,d,J=13.2Hz), 7.29(10H,m), 9.81(1H,s).

MS (FAB) m/z: 309 [(M+H)<sup>+</sup>].

[Referential Example 265] 1,4-Dibenzyl-2-[2-(1-piperidinyl)ethyl]piperazine

In methanol (10 mL) were dissolved 1,4-dibenzyl-2-(formylmethyl)piperazine (600 mg) and piperidine (200 mg). After stirring for 30 minutes, the solvent was concentrated under reduced pressure. The concentrate was dissolved in methanol (10 mL), followed by the addition of sodium borohydride (147 mg). The resulting mixture was stirred. Five hours later, the solvent was distilled off under reduced pressure. Chloroform was added to the residue and the mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 10:1 → 5:1), whereby the title compound (640 mg) was obtained as a colorless oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.42 (2H, m), 1.57 (4H, m), 1.85 (2H, m), 2.22-2.70 (13H, m), 3.22 (1H, d,  $J=13.5\text{Hz}$ ), 3.46 (2H, Abq,  $J=13.0\text{Hz}$ ), 3.99 (1H, d,  $J=13.2\text{Hz}$ ), 7.30 (10H, m).

MS (FAB)  $m/z$ : 378 [ $(\text{M}+\text{H})^+$ ].

[Referential Example 266] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-(1-piperidinyl)ethyl]piperazine

To 1,4-dibenzyl-2-[2-(1-piperidinyl)ethyl]piperazine (740 mg) was added 10% palladium-carbon (100 mg). The resulting mixture was dissolved in acetic acid (5.0 ml), followed by stirring under a hydrogen gas stream of 1

atmospheric pressure. Twenty hours later, the palladium was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in methylene chloride (10 mL), followed by the addition of triethylamine (595 mg). To the resulting mixture, 5-chloro-1-phenylsulfonylindol-2-sulfonyl chloride (765 mg) was added dropwise over 90 minutes and stirring was continued at room temperature. After 19 hours, chloroform was added and the resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol : isopropylamine = 500:75:1), whereby the title compound (335 mg) was obtained as a colorless oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.46-1.86(8H,m), 2.50-3.19(11H,m), 3.74(2H,m), 7.13-7.57(6H,m), 7.99(1H,d,J=9.5Hz), 8.02(1H,d,J=8.3Hz), 8.22(1H,d,J=9.0Hz).

MS (FAB)  $m/z$ : 551  $[(\text{M}+\text{H})^+]$ .

[Referential Example 267] 1,4-Dibenzyl-2-[2-(2-methoxyethyl)aminoethyl]piperazine

In the same manner as in Referential Example 265, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.84 (2H,m), 2.22 (3H,m), 2.51-2.81 (8H,m),  
3.23 (1H,d,J=14.4Hz), 3.35 (3H,s), 3.41-3.52 (4H,m),  
4.02 (1H,d,J=13.2Hz), 7.30 (10H,m).

MS (FAB)  $m/z$ : 368 ( $\text{M}+\text{H}$ ) $^+$ .

5 [Referential Example 268]

2-[2-[N-(tert-Butoxycarbonyl)-(2-methoxyethyl)amino]ethyl]-  
1,4-dibenzyl-piperazine

To 1,4-dibenzyl-2-[2-[(2-methoxyethyl)amino]ethyl]piperazine (540 mg) was added di-  
10 tert-butyl dicarbonate (353 mg). The resulting mixture was  
dissolved in methylene chloride (10 mL), followed by the  
addition of triethylamine (223 mg). After stirring for 3  
days, the reaction was terminated. The solvent was  
concentrated under reduced pressure. The residue was  
15 purified by chromatography on a silica gel column  
(methylene chloride : methanol = 100:1), whereby the title  
compound (610 mg) was obtained as a colorless oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40 (9H,s), 1.87 (2H,m), 2.21 (3H,m),  
2.53 (2H,m), 2.68 (2H,m), 3.22-3.52 (9H,m), 3.29 (3H,s),  
20 4.03 (1H,d,J=13.5Hz), 7.30 (10H,m).

MS (FAB)  $m/z$ : 468 [ $\text{M}+\text{H}$ ] $^+$ .

[Referential Example 269] 3-[2-[N-(tert-Butoxycarbonyl)-N-  
(2-methoxyethyl)amino]ethyl]-1-[(5-chloro-1-  
phenylsulfonylindol-2-yl)sulfonyl]piperazine

To 2-[2-[N-(tert-butoxycarbonyl)-2-methoxyethyl)amino]ethyl]-1,4-dibenzyl-piperazine (610 mg) was added 10% palladium-carbon (100 mg). The resulting mixture was dissolved in methanol (10 mL), followed by stirring under a hydrogen gas stream of 1 atmospheric pressure. After 3 days, palladium was filtered off and the solvent was concentrated under reduced pressure. The residue was dissolved in methylene chloride (10 mL), followed by the addition of triethylamine (390 mg). To the resulting mixture, 5-chloro-1-phenylsulfonylindole-2-sulfonyl chloride (503 mg) was added dropwise over 30 minutes. Stirring was continued at room temperature. After 22 hours, chloroform was added and the resulting mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : methanol = 25:1), whereby the title compound (490 mg) was obtained as a colorless oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45(9H,s), 1.46-3.76(15H,m), 3.31(3H,s), 7.21-7.56(6H,m), 8.01(2H,d,J=7.4Hz), 8.22(1H,d,J=9.1Hz).

MS (FAB)  $m/z$ : 641  $[(\text{M}+\text{H})^+]$ .

[Referential Example 270] Ethyl 5-hydrazino-3-(pyridin-4-yl)-1,2,4-triazine-6-carboxylate

At room temperature, ethyl 2,5-dihydro-5-oxo-3-(pyridin-4-yl)-1,2,4-triazine-6-carboxylate (246 mg) was added to phosphorus oxychloride (3 ml) in one portion, followed by stirring for 5 minutes. The reaction mixture was then heated to 90°C and stirred for 6 hours. After completion of the reaction, the solvent was distilled off. The residue was successively added with ice water, a saturated aqueous solution of sodium bicarbonate and diethyl ether. The organic layer thus separated was dried over anhydrous magnesium sulfate. The desiccant was removed by filtration. To the filtrate was added dioxane (50 ml), followed by cooling to 0°C. Hydrazine monohydrate (146  $\mu$ l) was added and the mixture was stirred for 1 minute. The solvent was distilled off and water was added to the residue. The pale yellow powder thus precipitated was collected by filtration and dried, whereby the title compound (52 mg) was obtained.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$ : 1.36(3H,t,J=7.3Hz), 4.41(2H,q,J=7.3Hz), 5.32(2H,br), 8.35(2H,br s), 8.81(2H,d,J=6.4Hz), 9.61(1H,br).

MS (FAB)  $m/z$ : 261 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 271] Ethyl 3-(pyridin-4-yl)-1,2,4-triazine-6-carboxylate

In ethanol (5 ml) was suspended ethyl 5-hydrazino-3-(pyridin-4-yl)-1,2,4-triazine-6-carboxylate (50 mg). To the resulting suspension, mercury (II) oxide (98 mg) was

added and the resulting mixture was heated under reflux for 9 hours. After completion of the reaction, the insoluble matter was removed through Celite filtration. The filtrate was concentrated and the concentrate was separated into layers by the addition of ethyl acetate and water. The organic layer thus obtained was dried over anhydrous magnesium sulfate. The filtrate was concentrated, whereby a crudely purified product of the title compound (23 mg, pale yellow powder) was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.52 (3H, t, J=7.3Hz), 4.61 (2H, q, J=7.3Hz), 8.45 (2H, d, J=6.4Hz), 8.89 (2H, d, J=6.4Hz), 9.33 (1H, s).  
MS (FAB) m/z: 231 (M+H)<sup>+</sup>.

[Referential Example 272] Ethyl bromo(pyridin-4-yl)acetate hydrochloride

At room temperature, ethyl pyridin-4-ylacetate (5.00g) was dissolved in acetic acid (100 ml), followed by the addition of a saturated acetic acid solution (50 ml) of hydrogen bromide. Bromine (1.56 ml) was slowly added dropwise to the resulting mixture. After stirring at room temperature for 1 hour, the reaction mixture was concentrated. Acetone was added to the concentrate. Colorless powder was collected by filtration, followed by drying. The resulting powder was extracted with ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and the filtrate was concentrated. The



residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 1:1), followed by the addition of 1N hydrochloric acid (in ethanol) to make the mixture acidic. The acidified solution was concentrated, whereby the title compound (colorless powder, 2.68 g) was obtained.

$^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$ : 1.20 (3H, t,  $J=7.3\text{Hz}$ ), 4.15-4.30 (2H, m), 6.28-6.29 (1H, m), 8.01 (2H, d,  $J=6.4\text{Hz}$ ), 8.92 (2H, d,  $J=6.4\text{Hz}$ ).  
MS (FAB)  $m/z$ : 244  $[(\text{M}+\text{H})^+, \text{Br}^{79}]$ , 246  $[(\text{M}+\text{H})^+, \text{Br}^{81}]$ .

[Referential Example 273] Ethyl (pyridin-4-yl)glyoxylate hydrate

Ethyl bromo(pyridin-4-yl)acetate hydrochloride (2.05 g) was dissolved in N,N-dimethylformamide (10 ml) at room temperature, followed by the addition of sodium azide (1.43 g). The resulting mixture was stirred for 30 minutes. After the addition of water and stirring, the insoluble matter was filtered off and the filtrate was concentrated. The residue was extracted with diethyl ether and saturated aqueous NaCl solution. The organic layer thus obtained was dried over anhydrous magnesium sulfate. The filtrate was concentrated and the residue was crystallized from methylene chloride, whereby the title compound (yellow powder, 300 mg) was obtained.

$^1\text{H-NMR}$  (DMSO- $\text{d}_6$ )  $\delta$ : 1.10 (3H, t,  $J=7.3\text{Hz}$ ), 4.05 (2H, d,  $J=7.3\text{Hz}$ ), 7.22 (2H, s), 7.48 (2H, d,  $J=5.9\text{Hz}$ ), 8.56 (2H, d,  $J=6.4\text{Hz}$ ).

MS (EI) m/z: 198 (M+18)<sup>+</sup>, 179 M<sup>+</sup>.

[Referential Example 274] Ethyl 2,5-dihydro-5-oxo-6-(pyridin-4-yl)-1,2,4-triazine-3-carboxylate

Ethyl thiooxamate (172 mg) was suspended in ethanol (5 ml) at 0°C, followed by the addition of hydrazine monohydrate (63 µl). While the resulting gas was suctioned, the resulting mixture was stirred for 30 minutes. Ethyl (pyridin-4-yl)glyoxylate hydrate (254 mg) was added to the reaction mixture and the mixture was stirred at room temperature for 30 minutes. After heating under reflux for 4 hours, the reaction mixture was concentrated. The yellow powder thus precipitated was collected by filtration and dried, whereby the title compound (140 mg) was obtained.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 1.36(3H,t,J=7.3Hz), 4.42(2H,d,J=7.3Hz), 8.08(2H,d,J=4.9Hz), 8.74(2H,br s).

MS (FAB) m/z: 247 (M+H)<sup>+</sup>.

[Referential Example 275] 2,5-Dihydro-5-oxo-6-(pyridin-4-yl)-1,2,4-triazine-3-carboxylic acid

In the same manner as in Referential Example 11, the title compound was synthesized.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub> with one drop of TFA) δ: 8.65(2H,d,J=5.4Hz), 8.88(1H,s), 9.00(2H,d,J=5.4Hz).

[Referential Example 276] 1-(4-Bromophenylsulfonyl)-4-(tert-butoxycarbonyl)piperazine

Diisopropylethylamine (4.00 ml) was added to a solution of 4-bromobenzenesulfonyl chloride (3.00 g) and 1-(tert-butoxycarbonyl)piperazine (2.40 g) in methylene chloride (50 ml) at room temperature. After stirring at room temperature for 30 minutes, the reaction mixture was concentrated under reduced pressure. The residue thus obtained was purified by chromatography on a silica gel column (hexane : ethyl acetate = 4:1 → 1:1), followed by reprecipitation in a hexane - methylene chloride system, whereby the title compound (4.47 g) was obtained as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.41 (9H, s), 2.97 (4H, t, J=5.1Hz), 3.51 (4H, t, J=5.1Hz), 7.61 (2H, d, J=8.8Hz), 7.69 (2H, d, J=8.8Hz). MS (FAB) m/z: 405 [(M+H)<sup>+</sup>, Br<sup>79</sup>], 407 [(M+H)<sup>+</sup>, Br<sup>81</sup>], 349 [(M+H-isobutene)<sup>+</sup>, Br<sup>79</sup>], 351 [(M+H-isobutene)<sup>+</sup>, Br<sup>81</sup>], 305 [(M+H-isobutene-CO<sub>2</sub>)<sup>+</sup>, Br<sup>79</sup>], 307 [(M+H-isobutene-CO<sub>2</sub>)<sup>+</sup>, Br<sup>81</sup>].

[Referential Example 277] 1-(tert-Butoxycarbonyl)-4-[4-(pyridin-4-yl)benzenesulfonyl]piperazine

To a solution of 1-(4-bromobenzenesulfonyl)-4-(tert-butoxycarbonyl)piperazine (1.00 g) in tetrahydrofuran (50 ml) were added diethyl(pyridin-4-yl)boron (470 mg), tetrabutylammonium bromide (480 mg), potassium hydroxide (625 mg), tetrakis(triphenylphosphine) palladium (285 mg) and water (800 μl) at room temperature. The resulting mixture

was heated under reflux for 1 hour. After allowed to cool down, the reaction mixture was added with ethyl acetate (50 ml) and water (100 ml). The water layer thus separated was extracted with ethyl acetate (50 ml). The organic layers were combined, washed with saturated aqueous NaCl solution (50 ml), dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (methylene chloride : ethyl acetate = 1:1), whereby the title compound (540 mg) was obtained as a colorless transparent viscous substance.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.41 (9H, s), 3.04 (4H, t,  $J=5.0\text{Hz}$ ), 3.54 (4H, t,  $J=5.0\text{Hz}$ ), 7.52 (2H, d,  $J=5.9\text{Hz}$ ), 7.79 (2H, d,  $J=8.8\text{Hz}$ ), 7.87 (2H, d,  $J=8.8\text{Hz}$ ), 8.74 (2H, d,  $J=5.9\text{Hz}$ ).

[Referential Example 278] 1-[(6-Chlorobenzo[b]thien-2-yl)sulfonyl]-3-(2-methylpropyl)piperazine

To a methylene chloride solution (30 ml) of 2-(2-methylpropyl)piperazine hydrochloride (353 mg) were added 6-chlorobenzo[b]thiophene-2-sulfonyl chloride (438 mg) and triethylamine (498 mg). The resulting mixture was stirred at room temperature for 3 hours. Distilled water and methylene chloride were added. The water layer thus obtained was extracted three times with methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected

to chromatography on a silica gel column (methanol :  
methylene chloride = 1:100), whereby the title compound  
(363 mg) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.78-0.94 (0.5H,m), 1.16-1.34 (0.5H,m),

5 1.40-1.54 (1H,m), 1.70 (3H,s), 1.71 (3H,s),

2.24 (1H,t,J=11.2Hz), 2.55 (1H,dt,J=3.4,11.2Hz), 2.92-

3.08 (2H,m), 3.52-3.62 (2H,m), 3.65-3.74 (1H,m),

4.92 (1H,d,J=8.3Hz), 7.43 (1H,dd,J=8.8,2.0Hz), 7.74 (1H,s),

7.81 (1H,d,J=8.8Hz), 7.85 (1H,d,J=2.0Hz).

10 MS (FAB)  $m/z$ : 383  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 385  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 279] 1-[(5-Bromopyrimidin-2-  
yl)carbonyl]-4-[(6-chlorobenzo[b]thiophen-2-yl)sulfonyl]-2-  
(2-methylpropyl)piperazine

To an N,N-dimethylformamide solution (60 ml) of 1-[(6-  
15 chlorobenzo[b]thiophen-2-yl)sulfonyl]-3-(2-  
methylpropyl)piperazine (2.55 mg) were added bromo-tris-  
pyrrolidino-phosphonium hexafluorophosphate (607 mg, 1.17  
mmol), (4-bromopyrimidin-2-yl)carboxylic acid (237 mg) and  
triethylamine (118 mg), followed by stirring at room  
20 temperature for 13 hours. After completion of the  
reaction, the solvent was distilled off under reduced  
pressure. Distilled water and methylene chloride were  
added to the residue. The water layer thus obtained was  
extracted three times with methylene chloride. The organic  
25 layers were combined and washed with distilled water.  
After drying over anhydrous magnesium sulfate, the solvent

was distilled under off under reduced pressure. The residue was subjected to chromatography on a silica gel column (methanol : methylene chloride = 1:100), followed by crystallization from ethyl acetate - diethyl ether, whereby the title compound (326 mg) was obtained as brown crystals.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.70-1.07(1H,m), 1.20-1.32(1H,m), 1.64-1.76(1H,m), 1.79(3H,s), 1.83(3H,s), 2.56-2.97(2H,m), 3.36-3.66(2H,m), 3.70-3.81(1H,m), 3.85-3.94(0.5H,m), 4.57-5.03(0.5H,m), 7.46(1H,dd,J=8.8,2.0Hz), 7.75(1H,s), 7.82(1H,d,J=8.8Hz), 7.88(1H,br), 8.58-8.72(2H,m).  
MS (FAB)  $m/z$ =555 ( $\text{M}^+$ ), 557 [ $(\text{M}+2)^+$ ], 559 [ $(\text{M}+4)^+$ ].

[Referential Example 280] 1-(tert-Butoxycarbonyl)-3,3-dimethylpiperazine

To a methylene chloride solution (5.0 ml) of 2,2-dimethylpiperazine (460 mg, 4.03 mmol) (J. Med. Chem., 1995, 38, 4389) was added di-tert-butyl dicarbonate (780  $\mu\text{l}$ ). The resulting mixture was stirred for 3 hours. The reaction mixture was diluted with methylene chloride and then added with saturated aqueous NaCl solution to separate into two layers. The water layer thus obtained was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crudely purified product was purified by chromatography on a silica gel column (methylene chloride : methanol = 10:1), whereby the title compound (360 mg) was obtained as a colorless oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.19(6H,s), 1.46(9H,s),  
2.93(2H,t,J=4.9Hz), 3.23(2H,s), 3.42-3.48(2H,br), 3.95-  
4.01(1H,s).

[Referential Example 281] 4-(tert-Butoxycarbonyl)-1-[(6-  
5 chloronaphthalen-2-yl)sulfonyl]-2,2-dimethylpiperazine

To a solution of 1-(tert-butoxycarbonyl)-3,3-  
dimethylpiperazine (125 mg) in methylene chloride (3.0 ml)  
were added triethylamine (90 ml) and 6-chloronaphthalene-2-  
sulfonyl chloride (167 mg). The resulting mixture was  
10 stirred at room temperature for 84 hours. The reaction  
mixture was diluted with methylene chloride and added with  
a saturated aqueous solution of sodium chloride to form two  
layers. The organic layer obtained by separation was dried  
over anhydrous sodium sulfate and concentrated under  
15 reduced pressure. The crudely purified product was  
purified by chromatography on a silica gel column (hexane :  
ethyl acetate = 8:1), whereby the title compound (155 mg)  
was obtained as a colorless solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.31(6H,s), 1.44(9H,s), 3.22(2H,br s),  
20 3.49-3.62(2H,br), 3.57-3.62(2H,br),  
7.56(1H,dd,J=8.8,2.0Hz), 7.79(1H,d,J=8.8Hz), 7.86(1H,s),  
7.87-7.92(3H,m), 8.36(1H,s).

[Referential Example 282] 1-[(6-Chloronaphthalen-2-  
25 yl)sulfonyl]-2,2-dimethylpiperazine hydrochloride

To a methylene chloride solution (0.5 ml) of 4-(tert-butoxycarbonyl)-1-[(6-chloronaphthalen-2-yl)sulfonyl]-2,2-dimethylpiperazine (140 mg) was added a saturated solution (0.5 ml) of hydrochloride in ethanol. The resulting mixture was stirred at room temperature for 14 hours. Ethanol was added to the reaction mixture. After the sufficient removal of hydrochloric acid by azeotropy, the residue was dried using a vacuum pump, whereby the title compound (119 mg) was obtained as a colorless solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 3.17(4H, br s), 3.50-3.95(4H, br), 7.44(2H, t, J=3.9Hz), 7.57(2H, d, J=8.8Hz), 7.66(1H, t, J=3.9Hz), 7.92(2H, d, J=8.8Hz), 8.36(1H, d, J=7.8Hz), 9.21(2H, d, J=3.9Hz). MS (FAB) m/z: 339 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 341 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 283] 4-(tert-Butoxycarbonyl)-2,2-dimethyl-1-[4-(pyridin-4-yl)benzoyl]piperazine

To a solution of 1-(tert-butoxycarbonyl)-3,3-dimethylpiperazine (173 mg) in a mixture of N,N-dimethylformamide (2.5 ml) and triethylamine (1.0 ml) was added (4-nitrophenyl) 4-(4-pyridyl)benzoate (330 mg). The resulting mixture was stirred at 60°C for 5 days. The reaction mixture was diluted with methylene chloride and then added with a saturated aqueous solution of sodium chloride to form two layers. The organic layer obtained by separation was washed with a saturated aqueous solution of sodium bicarbonate and an aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and



concentrated under reduced pressure. The crudely purified product was purified by chromatography on a silica gel column (methylene chloride : methanol = 50:1), whereby the title compound (199 mg) was obtained as colorless amorphous.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49(9H,s), 1.61(6H,s), 3.45-3.56(6H,m), 7.50(2H,d,J=5.9Hz), 7.51(2H,d,J=7.8Hz), 7.67(2H,d,J=7.8Hz), 8.69(1H,d,J=5.9Hz).

MS (FAB)  $m/z$ : 369 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 284] 1,4-bis(tert-Butoxycarbonyl)-2-(2-hydroxyethyl)piperazine

In methanol (200 ml) and concentrated hydrochloric acid (5.4 ml) was dissolved 1,4-dibenzyl-2-(2-hydroxyethyl)piperazine (19.2 g). Palladium hydroxide (1.02 g) was then suspended in the resulting solution. The resulting suspension was vigorously shaken at room temperature for 15.5 hours under a hydrogen gas atmosphere of 1 atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue thus obtained was added with methylene chloride (250 ml), methanol (50 ml) and diisopropylethylamine (20.0 ml) to dissolve the former in the latter. Under ice cooling, di-tert-butyl dicarbonate (27.0 g) was added and the resulting mixture was stirred at room temperature for 18.5 hours. The solvent was distilled off under reduced pressure. The residue was subjected to chromatography on a

silica gel column (hexane : ethyl acetate = 9:1 → hexane : ethyl acetate = 1:1). Hexane was added to the residue to solidify the same, whereby the title compound (16.1 g) was obtained as colorless powder.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.46, 1.48 (18H, each s), 1.30-1.90 (2H, m), 2.70-4.40 (10H, m).

MS (FAB)  $m/z$ : 331 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 285] 1,4-Bis(tert-butoxycarbonyl)-2-formylmethylpiperazine

10 In methylene chloride (150 ml) was dissolved 1,4-bis(tert-butoxycarbonyl)-2-(2-hydroxyethyl)piperazine. Under ice cooling, N-methylmorpholine (2.14 g) and tetra-n-propylammonium perruthenate (0.97 g) were added to the reaction mixture, followed by stirring at room temperature

15 for 17 hours. The reaction mixture was then distilled off under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane : ethyl acetate = 9:1 to 2:1), whereby the title compound (3.11 g) was obtained as colorless powder.

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45 (18H, s), 2.50-3.10 (15H, m), 3.70-4.20 (3H, m), 4.66 (1H, br), 9.76 (1H, s).

MS (FAB)  $m/z$ : 329 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 286] 1,4-Bis(tert-butoxycarbonyl)-2-[3-(thien-2-yl)-2-propenyl]piperazine

In tetrahydrofuran (50 ml) was dissolved 1,4-bis(tert-butoxycarbonyl)-2-formylmethylpiperazine (1.01 g). Under ice cooling, a solution of [(thien-2-yl)methyl]phosphonium (1.62 g) in chloroform (100 ml) was added to the resulting solution, followed by the dropwise addition of 1,8-diazabicyclo[5.4.0]-7-undecene (620  $\mu$ l). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was distilled under reduced pressure.

The residue was subjected to chromatography on a silica gel column (hexane : ethyl acetate = 9:1 to 2:1), whereby the title compound (1.13 g) was obtained as a pale yellow oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30-1.50(18H,m), 2.30-2.50(1H,m), 2.50-3.10(4H,m), 3.40-4.60(4H,m), 5.45-6.05(1H,m), 6.50-6.65(1H,m), 6.85-7.30(3H,m).

MS (FAB)  $m/z$ : 409 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 287] 1,4-Bis(tert-butoxycarbonyl)-2-[3-(thien-2-yl)propyl]piperazine

In methanol (70 ml) was dissolved 1,4-bis(tert-butoxycarbonyl)-2-[3-(thien-2-yl)-2-propenyl]piperazine (1.01 g). In the resulting solution was suspended 10% palladium-carbon (50% wet, 431 mg), followed by vigorous shaking at room temperature for 6 hours under a hydrogen gas atmosphere of 1 atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane : ethyl

acetate = 9:1 to 2:1), whereby the title compound (975 mg) was obtained as colorless powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45(9H,s), 1.46(9H,s), 1.50-1.80(4H,m), 2.70-3.00(5H,m), 3.80-4.20(4H,m), 7.75-7.80(1H,m), 7.85-  
5 7.95(1H,m), 7.10(1H,d,J=5.1Hz).

MS (FAB) m/z: 411 (M+H)<sup>+</sup>.

[Referential Example 288] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[3-(thien-2-yl)propyl]piperazine

10 In the same manner as in Referential Example 220, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.35-1.80(4H,m), 2.55-2.65(1H,m), 2.75-3.10(6H,m), 3.77(2H,t,J=10.9Hz), 6.70-6.80(1H,m), 6.85-6.95(1H,m), 7.05-7.15(1H,m), 7.35-7.0(4H,m), 7.50-  
15 7.60(2H,m), 8.00-8.10(2H,m), 8.22(1H,d,J=9.3Hz).

MS (FAB) m/z: 564 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 566 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 289] 1,4-Bis(tert-butoxycarbonyl)-2-[3-(3,4-dimethoxyphenyl)-2-propenyl]piperazine

20 In the same manner as in Referential Example 286, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.40-1.50(18H,m), 2.35-3.10(5H,m), 3.75-4.30(10H,m), 5.50-6.05(1H,m), 6.30-6.50(1H,m), 6.75-6.90(3H,m).

MS (FAB) m/z: 463 (M+H)<sup>+</sup>.

[Referential Example 290] 1,4-Bis(tert-butoxycarbonyl)-2-[3-(3,4-dimethoxyphenyl)propyl]piperazine

In the same manner as in Referential Example 287, the title compound was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.45(18H,s), 1.20-1.70(4H,m), 2.50-3.05(5H,m), 3.70-4.20(10H,m), 6.65-6.80(3H,m).  
MS (FAB)  $m/z$ : 465 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 291] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[3-(3,4-  
10 dimethoxyphenyl)propyl]piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30-1.70(4H,m), 2.50-2.65(3H,m), 2.75-3.05(4H,m), 3.70-3.90(8H,m), 6.0-6.70(2H,m), 6.75-  
15 6.80(1H,m), 7.35-7.50(4H,m), 7.50-7.60(2H,m), 8.02(2H,d,J=8.1Hz), 8.22(1H,d,J=9.0Hz).  
MS (FAB)  $m/z$ : 619 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 621 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 292] 1,4-Bis(tert-butoxycarbonyl)-2-(2-bromoethyl)piperazine

20 In methylene chloride (70 ml) were dissolved 1,4-bis(tert-butoxycarbonyl)-2-(2-hydroxyethyl)piperazine (2.01 g) and triphenylphosphine (1.98 g). Under ice cooling, carbon tetrabromide (3.07 g) was added to the resulting solution, followed by stirring at room temperature for 2.5  
25 hours. The reaction mixture was extracted with a 10%

aqueous solution of sodium thiosulfate. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (hexane : ethyl acetate = 4:1) using as a carrier silica gel, whereby the title compound (2.20 g) was obtained as colorless powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47, 1.48 (18H, each s), 2.00-2.20 (2H, m), 2.70-3.00 (3H, m), 3.30-3.45 (2H, m), 3.80-4.40 (4H, m).

[Referential Example 293] 1,4-Bis(tert-butoxycarbonyl)-2-[2-[(pyrrolidin-1-yl)sulfonyl]ethyl]piperazine

Sodium sulfite (1.68 g) was dissolved in water (90 ml). Under ice cooling, a solution of 1,4-bis(tert-butoxycarbonyl)-2-(2-bromoethyl)piperazine (2.20 g) in N,N-dimethylformamide (90 ml) was added to the reaction mixture, followed by stirring at 50°C for 15 hours. The reaction mixture was then concentrated under reduced pressure. The residue was added with ethanol and the insoluble matter was filtered off. The filtrate was concentrated under reduced pressure, whereby the crudely purified product (2.98 g) was obtained as a colorless paste. The crudely purified product was then dissolved in N,N-dimethylformamide (10 ml). Under ice cooling, thionyl chloride (407  $\mu\text{l}$ ) was added dropwise, followed by stirring at 0°C for 0.5 hour and at room temperature for 1 hour. Ice water (40 ml) was poured into the reaction mixture.

After the removal of the insoluble matter, the residue was dried. The residue was then dissolved in methylene chloride. The resulting solution was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby pale yellow oil (524.9 mg) was obtained. The crudely purified product was then dissolved in methylene chloride (10 ml), followed by the addition of diisopropylethylamine (500  $\mu$ l) and pyrrolidine (220  $\mu$ l) under ice cooling. The resulting mixture was stirred at room temperature for 19 hours. The reaction mixture was distilled under reduced pressure. The residue was subjected to column chromatography (hexane : ethyl acetate = 1:1) using silica gel as a carrier, whereby the title compound (122 mg) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47, 1.47(18H, each s), 1.85-2.20(6H, m), 2.70-3.10(5H, m), 3.30-3.40(4H, m), 3.80-4.30(4H, m).

[Referential Example 294] 1-[(5-Chloro-1-phenylsulfonylindol-2-yl)sulfonyl]-3-[2-[(pyrrolidin-1-yl)sulfonyl]ethyl]piperazine

In the same manner as in Referential Example 220, the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.80-2.00(6H, m), 2.60-2.70(1H, m), 2.80-3.1(6H, m), 3.30-3.40(4H, m), 3.65-3.85(2H, m), 7.40-7.50(4H, m), 7.50-7.60(2H, m), 8.01(2H, d,  $J=7.8\text{Hz}$ ), 8.22(2H, d,  $J=8.3\text{Hz}$ ).

MS (FAB)  $m/z$ : 601  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 603  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 295] 4-(Chloro-2-methoxyphenyl)methanol

In tetrahydrofuran (100 ml) was dissolved 4-chloro-2-methoxyphenylcarboxylic acid (20.1 g), followed by purging  
5 with argon. A borane-methylsulfide complex (11.0 ml) was added dropwise to the reaction mixture. After completion of the dropwise addition, when reflux due to the emission of heat generated by the reaction stopped, stirring was conducted at room temperature for 2 hours. Under ice  
10 cooling, water was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The organic layer thus obtained was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate  
15 and distilled under reduced pressure to remove the solvent, whereby the title compound (17.6 g) was obtained as pale yellow powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.25(1H,s), 3.85(3H,s), 4.63(2H,s),  
6.86(1H,d,J=1.8Hz), 6.92(1H,dd,J=8.2,1.8Hz),  
20 7.21(1H,d,J=8.2Hz).

[Referential Example 296] 4-Chloro-1-formyl-2-methoxybenzene

In methylene chloride (80 ml) was dissolved (4-chloro-2-methoxyphenyl)methanol (3.69 g). Under ice cooling,  
25 molecular sieve 4A (4.57 g), N-methylmorpholine (2.81 g) and tetra-n-propylammonium perruthenate (420 mg) were added



to the resulting solution, followed by stirring at room temperature for 2.5 hours. The reaction mixture was distilled under reduced pressure. The residue was subjected to chromatography on a silica gel column (hexane : ethyl acetate = 9:1), whereby the title compound (3.07 g) was obtained as pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.94 (3H,s), 6.99 (1H,d,J=2.0Hz), 7.00-7.05 (1H,m), 7.77 (1H,d,J=8.3Hz), 10.39 (1H,s).

[Referential Example 297] 4-Chloro-2-methoxystyrene

In tetrahydrofuran (50 ml) was suspended methyltriphenylphosphonium bromide (5.03 g), followed by purging with argon. Under ice cooling, n-butyl lithium (a 1.59 mole solution, hexane) (9.80 ml) was added dropwise over 30 minutes. After completion of the dropwise addition, stirring was conducted at room temperature for 30 minutes. Under ice cooling, a solution of 4-chlorobenzaldehyde (2.02 g) in tetrahydrofuran (15 ml) was added dropwise to the reaction mixture. After completion of the dropwise addition, stirring was conducted at room temperature for 3.5 hours. Then, water was added to the reaction mixture under ice cooling. The reaction mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (hexane : ethyl

acetate = 9:1), whereby the title compound (1.51 g) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.83(3H,s), 5.26(1H,dd,J=11.2,1.5Hz),  
5.70(1H,dd,J=17.8,1.2Hz), 6.80-7.00(3H,m),  
5 7.37(1H,d,J=8.3Hz).

MS (FAB)  $m/z$ : 169  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 171  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 298] (4-Chloro-2-methoxystyryl)sulfonyl chloride

Sulfuryl chloride (1.66 ml) was charged in a  
10 container, followed by purging with argon. Under ice cooling, N,N-dimethylformamide (1.7 ml) was added, followed by stirring at room temperature for 40 minutes. To the reaction mixture was added 4-chloro-2-methoxystyrene (2.05 g) and the resulting mixture was stirred at 90°C for 3  
15 hours. Ice was added and the resulting mixture was extracted with methylene chloride. The extract was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to column  
20 chromatography (hexane : ethyl acetate = 9:1) using as a carrier silica gel, whereby the title compound (885 mg) was obtained as a pale yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.96(3H,s), 6.98(1H,d,J=2.0Hz),  
7.03(1H,dd,J=8.3,2.0Hz), 7.38(1H,d,J=8.3Hz),  
25 7.50(1H,d,J=15.1Hz), 7.78(1H,d,J=15.1Hz).

MS (FAB)  $m/z$ : 266  $[(M+H)^+, Cl^{35}+Cl^{35}]$ .

[Referential Example 299] 1-(tert-Butoxycarbonyl)-4-[(E)-4-chloro-2-methoxystyrylsulfonyl]piperazine

In the same manner as in Referential Example 129, the title compound was synthesized.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 1.44 (9H, s), 3.10-3.20 (4H, m), 3.50-3.60 (4H, m), 3.91 (3H, s), 6.82 (1H, d,  $J=15.6$  Hz), 6.94 (1H, d,  $J=2.0$  Hz), 6.97 (1H, dd,  $J=8.3, 2.0$  Hz), 7.33 (1H, d,  $J=8.3$  Hz), 7.56 (1H, d,  $J=15.6$  Hz).

MS (FAB)  $m/z$ : 416  $[(M+H)^+, Cl^{35}]$ , 418  $[(M+H)^+, Cl^{37}]$ .

[Referential Example 300] 1-(5-Bromopyrimidin-2-yl)-4-[(E)-4-chloro-1-methoxystyryl)sulfonyl]piperazine

In methylene chloride (10 ml) was dissolved 1-(tert-butoxycarbonyl)-4-[(E)-4-chloro-1-methoxystyryl)sulfonyl]piperazine (690 mg). Under ice cooling, trifluoroacetic acid (1.0 ml) was added dropwise to the resulting solution, followed by stirring at room temperature for 1 hour. Methylene chloride (10 ml) was added further to the reaction mixture and they were stirred at 0°C for 23 hours and at room temperature for 2 hours. The solvent was distilled off under reduced pressure. The residue was extracted with methylene chloride and a saturated aqueous solution of sodium bicarbonate. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The

resulting residue, that is, (5-bromopyrimidin-2-yl)carboxylic acid (467 mg) was dissolved in a mixture of N,N-dimethylformamide (15 ml) and methylene chloride (15 ml), followed by the successive addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (366 mg), 1-hydroxybenzotriazole hydrate (266 mg) and diisopropylethylamine (1.01 ml) under ice cooling. The resulting mixture was stirred at room temperature for 25 hours. The solvent was then distilled off under reduced pressure. The residue was extracted with methylene chloride and a saturated aqueous solution of sodium bicarbonate. The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (hexane : ethyl acetate = 1:1 to 1:2) using as a carrier silica gel, whereby the title compound (629 mg) was obtained as colorless powder.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.22 (2H, t,  $J=4.5\text{Hz}$ ), 3.33 (2H, t,  $J=4.6\text{Hz}$ ), 3.52 (2H, t,  $J=4.4\text{Hz}$ ), 3.90-3.95 (2H, m), 6.83 (1H, d,  $J=15.6\text{Hz}$ ), 6.95 (1H, s), 6.99 (1H, d,  $J=8.3\text{Hz}$ ), 7.33 (1H, d,  $J=8.3\text{Hz}$ ), 7.56 (1H, d,  $J=15.6\text{Hz}$ ), 8.80-8.90 (2H, m).

MS (FAB)  $m/z$ : 501 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ,  $\text{Br}^{79}$ ], 505 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ,  $\text{Br}^{81}$  and  $\text{Cl}^{37}$ ,  $\text{Br}^{79}$ ], 507 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ,  $\text{Br}^{81}$ ].

[Referential Example 301] 2,cis-6-Bis(methoxycarbonylmethyl)-1-(5-bromopyrimidin-2-yl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In a mixture of methylene chloride (30 ml) and N,N-dimethylformamide (200  $\mu$ l) was dissolved 5-bromo-2-pyrimidinecarboxylic acid (736 mg), followed by purging with argon. Under an argon atmosphere and ice cooling, oxalyl chloride (0.40 ml) was added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature for 0.5 hour. The reaction mixture thus obtained was designated as "Reaction Mixture A".

In methylene chloride (50 ml) was dissolved 2,cis-6-bis(methoxycarbonylmethyl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine (529 mg). Diisopropylethylamine (2.00 ml) was added to the reaction mixture under ice cooling, followed by purging with argon. Reaction Mixture A prepared in advance was then added dropwise under ice cooling and the resulting mixture was stirred at room temperature for 11 hours. The reaction mixture was extracted with a saturated aqueous solution of sodium bicarbonate. The organic layer was washed successively with dilute hydrochloric acid and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to column chromatography (0.5% ~ 1% methanol - methylene chloride) using as a carrier silica gel. The

solvent was then distilled off under reduced pressure. A small amount of methylene chloride was added to the residue for crystallization, whereby the title compound (432 mg) was obtained as pale yellow powder.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.40-3.00 (6H,m), 3.57-3.70 (8H,m), 3.90-4.00 (1H,m), 4.90-5.00 (1H,m), 7.70-7.75 (1H,m), 7.80-7.85 (1H,m), 8.15-8.30 (3H,m), 8.52 (1H,s), 9.07 (2H,s).

[Referential Example 302] 1-(5-Bromopyrimidin-2-yl)-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(methoxycarbonylmethyl)piperazine

In the same manner as in Referential Example 12, the title compound was synthesized.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.40-3.25 (5H,m), 3.45-3.55 (1H,m), 3.67, 3.72 (3H,each s), 3.70-5.30 (4H,m), 7.60 (1H,dd,J=8.6,1.7Hz), 7.70-7.75 (1H,m), 7.90-7.95 (3H,m), 8.25-8.30 (1H,m), 8.80, 8.81 (2H,each s).

MS (FAB) m/z: 567 [(M+H)<sup>+</sup>, Cl<sup>35</sup>, Br<sup>79</sup>], 569 [(M+H)<sup>+</sup>, Cl<sup>35</sup>, Br<sup>81</sup> and Cl<sup>37</sup>, Br<sup>79</sup>], 571 [(M+H)<sup>+</sup>, Cl<sup>37</sup>, Br<sup>81</sup>].

[Referential Example 303] 1-(tert-Butoxycarbonyl)-2-[2-(tert-butyldiphenylsilyloxy)ethyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In N,N-dimethylformamide (15 ml) was dissolved 1-tert-butoxycarbonyl-4-[(6-chloronaphthalen-2-yl)sulfonyl]-2-(2-hydroxyethyl)piperazine (739 mg) and imidazole (226 mg).

Under ice cooling, tert-butylchlorodiphenylsilane (0.70 ml)

was added to the resulting solution, followed by stirring at room temperature for 23 hours. The reaction mixture was distilled off under reduced pressure. The residue was extracted with methylene chloride and a saturated aqueous solution of sodium bicarbonate. The organic layer thus obtained was washed with dilute hydrochloric acid and saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography (hexane : ethyl acetate = 2:1 ~ :2) using as a carrier silica gel, whereby the title compound (804 mg) was obtained as a pale yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.06(9H,s), 1.31(9H,s), 1.90-2.00(2H,m), 2.20-2.30(1H,m), 2.30-2.40(1H,m), 2.95-3.05(1H,m), 3.60-3.80(4H,m), 3.85-4.00(1H,m), 4.35-4.45(1H,m), 7.35-7.45(6H,m), 7.55-7.60(1H,m), 7.65-7.75(5H,m), 7.85-7.95(3H,m), 8.26(1H,s).

MS (FAB) m/z: 693 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 695 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 304] 3-[2-(tert-Butyldiphenylsilyloxy)ethyl]-1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In nitrobenzene (5.0 ml) was dissolved 1-(tert-butoxycarbonyl)-2-[2-(tert-butyldiphenylsilyloxy)ethyl]-4-(6-chloronaphthalen-2-yl)piperazine (91.2 mg), followed by stirring at 170 to 185°C for 10.5 hours. The reaction mixture was subjected to chromatography on a silica gel

column (methylene chloride ~ 5% methanol - methylene chloride), whereby the title compound (43 mg) was obtained as a pale yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (9H, s), 1.50-1.65 (2H, m), 2.05-  
 5 2.15 (1H, m), 2.35-2.45 (1H, m), 2.85-3.00 (3H, m), 3.65-  
 3.75 (4H, m), 7.35-7.45 (6H, m), 7.55-7.60 (1H, m), 7.60-  
 7.65 (4H, m), 7.70-7.80 (1H, m), 7.85-7.95 (3H, m), 8.28 (1H, s).  
 MS (FAB) m/z: 593 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 595 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 305]

10 1-(5-Bromopyrimidin-2-yl)-2-[2-(tert-  
 butyldiphenylsilyloxy)ethyl]-4-[(6-chloronaphthalen-2-  
 yl)sulfonyl]piperazine

In a similar manner to Referential Example 12, the title compound was synthesized.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.90, 1.08 (9H, each s), 2.00-2.20 (2H, m),  
 2.30-2.60 (2H, m), 3.15-5.20 (7H, m), 7.35-7.60 (10H, m), 7.65-  
 7.75 (2H, m), 7.85-7.95 (3H, m), 8.20-8.30 (1H, m), 8.62,  
 8.79 (2H, each s).

MS (FAB) m/z: 777 [(M+H)<sup>+</sup>, Cl<sup>35</sup>, Br<sup>79</sup>], 779 [(M+H)<sup>+</sup>, Cl<sup>35</sup>,  
 20 Br<sup>81</sup> and Cl<sup>37</sup>, Br<sup>79</sup>], 781 [(M+H)<sup>+</sup>, Cl<sup>37</sup>, Br<sup>81</sup>].

[Referential Example 306] 2,cis-6-

Bis(methoxycarbonylmethyl)-4-[(6-chlorobenzo[b]thien-2-  
 yl)sulfonyl]piperazine and

2,trans-6-bis(methoxycarbonylmethyl)-4-[(6-  
 25 chlorobenzo[b]thien-2-yl)sulfonyl]piperazine



In the same manner to Referential Example 192, the title compound were synthesized.

Instrumental data of 2,cis-6-Bis(methoxycarbonylmethyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.15-2.45(6H,m), 2.90(1H,br), 3.25-3.35(2H,m), 3.65-3.75(2H,m), 3.70(6H,s), 7.43(1H,dd,J=8.5,1.7Hz), 7.75(1H,s), 7.82(1H,d,J=8.8Hz), 7.85-7.90(1H,m).

MS (FAB)  $m/z$ : 461  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 463  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

10 Instrumental data of 2,trans-6-Bis(methoxycarbonylmethyl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.50-2.65(6H,m), 2.85-2.95(2H,m), 3.20-3.25(2H,m), 3.50-3.55(2H,m), 3.70(6H,s), 7.43(1H,dd,J=8.6,1.7Hz), 7.74(1H,s), 7.82(1H,d,J=8.8Hz), 15 7.86(1H,br s).

MS (FAB)  $m/z$ : 461  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 463  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 307]

2,cis-6-Bis(methoxycarbonylmethyl)-1-(5-bromopyrimidin-2-yl)-4-[(6-chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

20 In the same manner as in Referential Example 301, the title compound was synthesized.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.65-2.80(3H,m), 2.90-3.00(2H,m), 3.00-3.10(1H,m), 3.65-3.75(2H,m), 3.68(3H,s), 3.73(3H,s), 4.00(1H,d,J=12.2Hz), 4.22(1H,d,J=9.8Hz), 5.20-5.30(1H,m), 25 7.40-7.50(1H,m), 7.77(1H,s), 7.80-7.90(2H,m), 8.80(2H,s).

[Referential Example 308] 1,4-Dibenzyl-2-hydroxymethylpiperazine

In tetrahydrofuran (42 ml) was suspended lithium aluminum hydride (1.04 g). After a suspension of 1,4-dibenzyl-2-ethoxycarbonylpiperazine (12.5 g) in tetrahydrofuran (300 ml) was added dropwise, stirring was conducted at room temperature for 89.5 hours. The reaction mixture was ice cooled and added with a saturated aqueous solution of sodium sulfate and a 3N aqueous solution of sodium hydroxide. The insoluble matter was filtered off and the solvent was distilled off under reduced pressure. The residue was dissolved in tetrahydrofuran. The resulting solution was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent.

Lithium aluminum hydride (1.5 g) was suspended in tetrahydrofuran (50 ml), followed by purging with argon. The reaction mixture was heated to 50°C. To the reaction mixture, a solution of the residue, which had been obtained above, in tetrahydrofuran (50 ml) was added dropwise, followed by heating under reflux for 4.5 hours. The reaction mixture was then heated under reflux for 4.5 hours after the addition of lithium aluminum hydride (0.87 g). Lithium aluminum hydride (0.87 g) was added again and the resulting mixture was heated under reflux for 4.5 hours. The reaction mixture was ice cooled and then added with a saturated aqueous solution of sodium sulfate and a 3N

aqueous solution of sodium hydroxide. The insoluble matter was filtered off and the solvent was distilled off under reduced pressure. The residue was dissolved in methylene chloride. The resulting solution was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was subjected to chromatography on a silica gel column (methylene chloride ~ 5% methanol - methylene chloride ), whereby the title compound (8.42 g) was obtained as a pale red oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.30-2.70 (5H,m), 2.90-3.00 (1H,m), 3.40-3.50 (4H,m), 3.58 (1H,d,J=13.2Hz), 3.90-4.10 (2H,m), 7.20-7.35 (10H,m).

MS (FAB)  $m/z$ : 297 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 309] 2-(tert-

Butyldiphenylsilyloxy)methyl-1,4-dibenzylpiperazine

In N,N-dimethylformamide (20 ml) were dissolved 1,4-dibenzyl-2-hydroxymethylpiperazine (1.11 g) and imidazole (347 mg). Under ice cooling, tert-butylchlorodiphenylsilane (1.17 ml, 1.24 g) was added to the reaction mixture, followed by stirring at room temperature for 14.5 hours. The solvent was distilled off under reduced pressure. The residue was extracted with ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The organic layer was then washed with saturated aqueous NaCl solution, dried over anhydrous sodium sulfate and distilled under reduced pressure to

remove the solvent. The residue was subjected to column chromatography (hexane : ethyl acetate = 9:1 → 8:2) using as a carrier silica gel, whereby the title compound (1.42 g) was obtained.

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.98 (9H, s), 2.15-2.30 (3H, m), 2.50-2.55 (1H, m), 2.60-2.70 (2H, m), 2.80-2.90 (1H, m), 3.24 (1H, d,  $J=13.7\text{Hz}$ ), 3.40-3.50 (2H, m), 3.60-3.70 (1H, m), 3.90-4.00 (2H, m), 7.15-7.45 (16H, m), 7.55-7.65 (4H, m).  
MS (FAB)  $m/z$ : 535 ( $\text{M}+\text{H}$ ) $^+$ .

10 [Referential Example 310] 3-(tert-Butyldiphenylsilyloxy)methyl-1-(6-chlorobenzo[b]thien-2-yl)piperazine

In the same manner as in Referential Example 192, the title compound was obtained.

15  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.02 (9H, s), 2.30-2.40 (1H, m), 2.45-2.65 (1H, m), 2.90-3.15 (3H, m), 3.50-3.70 (4H, m), 7.35-7.45 (7H, m), 7.55-7.65 (4H, m), 7.71 (1H, s), 7.75-7.85 (2H, m).  
MS (FAB)  $m/z$ : 585 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 587 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 311] 1-(5-Bromopyrimidin-2-yl)carbonyl-2-(tert-butyldiphenylsilyloxymethyl-4-(6-chlorobenzo[b]thien-2-yl)piperazine

In the same manner as in Referential Example 12, the title compound was obtained.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.02, 1.08 (9H, each s), 2.50-2.80 (2H, m), 2.95-3.70 (2H, m), 3.80-4.25 (4H, m), 4.55-5.10 (1H, m), 7.35-

7.50 (7H, m), 7.50-7.55 (1H, m), 7.60-7.65 (1H, m), 7.70-7.90 (5H, m), 8.65, 8.81 (2H, s).

MS (FAB)  $m/z$ : 769 [(M+H)<sup>+</sup>, Cl<sup>35</sup>, Br<sup>79</sup>], 771 [(M+H)<sup>+</sup>, Cl<sup>35</sup>, Br<sup>81</sup> and Cl<sup>37</sup>, Br<sup>79</sup>], 773 [(M+H)<sup>+</sup>, Cl<sup>37</sup>, Br<sup>81</sup>].

5 [Referential Example 312] 1,4-Dibenzyl-2-(2-hydroxyethyl)piperazine

In the same manner as in Referential Example 308, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.80-1.90 (1H, m), 2.00-2.10 (1H, m), 2.25-2.35 (2H, m), 2.35-2.45 (1H, m), 2.45-2.55 (1H, m), 2.60-2.70 (1H, m), 2.75-2.85 (1H, m), 2.85-2.95 (1H, m), 3.39 (1H, d, J=12.7 Hz), 3.49 (1H, d, J=1.5 Hz), 3.70-3.80 (1H, m), 3.80-3.90 (1H, m), 4.16 (1H, d, J=12.7 Hz), 7.20-7.40 (10H, m).

15 [Referential Example 313] 2-[2-(tert-Butyldiphenylsilyloxy)ethyl]-1,4-dibenzylpiperazine

In the same manner as in Referential Example 309, the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.99 (9H, s), 1.75-1.95 (2H, m), 2.10-2.20 (3H, m), 2.40-2.50 (1H, m), 2.50-2.65 (3H, m), 3.10-3.20 (1H, m), 3.30-3.50 (2H, m), 3.60-3.75 (2H, m), 3.83 (1H, d, J=13.2 Hz), 7.15-7.25 (10H, m), 7.25-7.40 (6H, m), 7.55-7.65 (4H, m).

MS (FAB)  $m/z$ : 549 (M+H)<sup>+</sup>.

[Referential Example 314] 3-[2-(tert-  
Butyldiphenylsilyloxy)ethyl]-1-[(6-chlorobenzo[b]thien-2-  
yl)sulfonyl]piperazine

In the same manner as in Referential Example 192, the  
5 title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.04 (9H, s), 1.50-2.00 (3H, m), 2.20-  
2.30 (1H, m), 2.50-2.60 (1H, m), 2.85-3.05 (3H, m), 3.65-  
3.80 (4H, m), 7.35-7.45 (7H, m), 7.60-7.65 (4H, m), 7.72 (1H, s),  
7.75-7.85 (2H, m).

10 MS (FAB) m/z: 599 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 601 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 315] 1-(5-Bromopyrimidin-2-yl)-2-[2-  
(tert-butyldiphenylsilyloxy)ethyl]-4-[(6-  
chlorobenzo[b]thien-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 12, the  
15 title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.90, 1.07 (9H, each s), 2.00-2.15 (2H, m),  
2.50-2.80 (2H, m), 3.15-5.25 (7H, m), 7.35-7.90 (16H, m), 8.64,  
8.81 (2H, each s).

MS (FAB) m/z: 783 [(M+H)<sup>+</sup>, Cl<sup>35</sup>, Br<sup>79</sup>], 785 [(M+H)<sup>+</sup>, Cl<sup>35</sup>,  
20 Br<sup>81</sup> and Cl<sup>37</sup>, Br<sup>79</sup>], 787 [(M+H)<sup>+</sup>, Cl<sup>37</sup>, Br<sup>81</sup>].

[Referential Example 316] 1-[(6-Chlorobenzo[b]thien-2-  
yl)sulfonyl]-3-(methoxycarbonylmethyl)piperazine

In the same manner as in Referential Example 192, the  
title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.30-2.50 (3H,m),  
 2.63 (1H,dt,J=3.4,11.0Hz), 2.90-3.10 (2H,m), 3.20-3.30 (1H,m),  
 3.60-3.70 (2H,m), 3.69 (3H,s), 7.44 (1H,dd,J=8.8,2.0Hz),  
 7.75 (1H,s), 7.82 (1H,d,J=8.3Hz), 7.85-7.90 (1H,m).

5 MS (FAB) m/z: 389 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 391 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 317] 1-[(5-Bromopyrimidin-2-yl)-4-  
 [(6-chlorobenzo[b]thien-2-yl)sulfonyl]-2-  
 (methoxycarbonylmethyl)piperazine

10 In the same manner as in Referential Example 12, the  
 title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.60-3.30 (5H,m), 3.50-5.40 (4H,m), 3.68,  
 3.73 (3H,each s), 7.45 (1H,dd,J=8.5,1.7Hz), 7.76,  
 7.77 (1H,each s), 7.80-7.85 (1H,m), 7.87 (1H,s), 8.83,  
 8.84 (2H,each s).

15 MS (FAB) m/z: 573 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 575 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 318] (2RS)-2-(N-tert-  
 Butoxycarbonylaminomethyl)-6-methoxycarbonyl-1,2,3,4-  
 tetrahydronaphthalene

20 In dimethylformamide (25 ml), (2RS)-6-methoxycarbonyl-  
 2-toluenesulfonyloxymethyl-1,2,3,4-tetrahydronaphthalene  
 (2.56 g) was dissolved. Sodium azide (0.92 g) was added to  
 the resulting solution, followed by stirring at an external  
 temperature of about 50°C for 14 hours. The reaction  
 mixture was concentrated under reduced pressure. The  
 25 concentrate was diluted with ethyl acetate, washed with

water and then dried over sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was dissolved in tetrahydrofuran (35 ml).

Triphenylphosphine (1.82 g) was added to the resulting

5 solution, followed by stirring at an external temperature of about 50°C for 21 hours. After about 28% aqueous ammonia (15 ml) was added and the resulting mixture was stirred for 3 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was extracted with  
10 diethyl ether. Dilute hydrochloric acid was added to the extract to make it acidic and water layer was separated.

To the resulting water layer, a dilute aqueous solution of sodium hydroxide was added to make it alkaline, followed by extraction with dichloromethane. The extract was dried  
15 over sodium sulfate and distilled under reduced pressure to remove the solvent. The resulting residue was dissolved in dichloromethane (15 ml). To the resulting solution, a solution of di-tert-butyl dicarbonate (1.80 g) in dichloromethane (5 ml) was added under ice cooling,

20 followed by stirring at room temperature for 2 hours. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (30 g of silica gel, dichloromethane ~  
dichloromethane : methanol = 50:1) and recrystallized from  
25 a mixed solvent of n-hexane and ethyl acetate, whereby colorless crystals (1.56 g, 71%) were obtained.



$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40-1.60 (1H,m), 1.46 (9H,s), 1.90-2.10 (2H,m), 2.50 (1H,dd,  $J=17.1, 10.7\text{Hz}$ ), 2.70-3.00 (3H,m), 3.10-3.30 (2H,m), 3.89 (3H,s), 4.68 (1H,br), 7.12 (1H,d,  $J=7.8\text{Hz}$ ), 7.70-7.80 (2H,m).

5 Elementary analysis for  $\text{C}_{18}\text{H}_{25}\text{NO}_4$

Calculated: C, 67.69; H, 7.89; N, 4.39.

Found: C, 67.78; H, 7.61; N, 4.12.

[Referential Example 319] 1-[[[(6RS)-6-(N-tert-butoxycarbonylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (5 ml), (2RS)-2-(N-tert-butoxycarbonylaminomethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene (0.14 g) was dissolved. To the resulting solution, 1N sodium hydroxide (0.50 ml) was added, followed by stirring at room temperature for 3 days and at an external temperature of about  $50^\circ\text{C}$  for 20 hours. 1N Sodium hydroxide (0.40 ml) was added further, followed by stirring at an external temperature of about  $50^\circ\text{C}$  for 2 days. After the reaction mixture was concentrated under reduced pressure, dichloromethane and dilute hydrochloric acid were added to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure to remove the solvent. The residue was dissolved in N,N-dimethylformamide (5 ml). To the resulting solution 1-[(6-chloronaphthalen-2-

yl)sulfonyl]piperazine hydrochloride (0.19 g), N-methylmorpholine (0.05 ml), 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (86.0 mg) and 1-hydroxybenzotriazole (71.0 mg) were added, followed by stirring at room temperature for 18 hours. After the reaction mixture was concentrated under reduced pressure, the concentrate was diluted with ethyl acetate and washed with water. The mixture was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (dichloromethane ~ dichloromethane : methanol = 100:1), whereby the title compound was obtained as a colorless oil (0.23 g, 86%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30-1.60 (1H,m), 1.45 (9H,s), 1.80-2.00 (2H,m), 2.43 (1H,dd,  $J=16.6, 10.7\text{Hz}$ ), 2.70-2.90 (3H,m), 3.00-3.20 (6H,m), 3.50-3.90 (4H,br), 4.69 (1H,br), 6.90-7.10 (3H,m), 7.59 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.75 (1H,dd,  $J=8.8, 2.0\text{Hz}$ ), 7.90-8.00 (3H,m), 8.30 (1H,s).

MS (FAB)  $m/z$ : 598 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{35}$ ], 600 [ $(\text{M}+\text{H})^+$ ,  $\text{Cl}^{37}$ ].

[Referential Example 320] (2RS)-2-(N-tert-Butoxycarbonylaminomethyl)-6-hydroxymethyl-1,2,3,4-tetrahydronaphthalene

In dichloromethane (10 ml), the (2RS)-2-(N-tert-butoxycarbonylaminomethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene (0.47 g) was dissolved. Aluminum diisobutylhydride (a 0.95M hexane solution, 3.60 ml) was

added dropwise to the resulting solution at an external temperature of  $-78^{\circ}\text{C}$ , followed by stirring for 90 minutes without changing the temperature. Methanol was added to the reaction mixture and the mixture was heated to room temperature. The insoluble matter was filtered off from filtration through Celite. The filtrate was concentrated under reduced pressure. The concentrate was diluted with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby colorless crystals (0.31 g, 72%) was obtained. A portion of the resulting crystals was recrystallized from a mixed solvent of hexane and ethyl acetate, whereby colorless crystals were obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.40-1.60 (1H,m), 1.46 (9H,s), 1.60-1.70 (1H,m), 1.90-2.00 (2H,m), 2.45 (1H,dd,  $J=16.6, 10.7\text{Hz}$ ), 2.70-2.90 (3H,m), 3.10-3.30 (2H,m), 4.62 (2H,d,  $J=5.9\text{Hz}$ ), 4.67 (1H,br), 7.00-7.20 (3H,m).

Elementary analysis for  $\text{C}_{17}\text{H}_{25}\text{NO}_3$

Calculated: C, 70.07; H, 8.65; N, 4.81.

Found: C, 70.21; H, 8.49; N, 4.75.

[Referential Example 321] 1-[[[(6RS)-6-(N-tert-Butoxycarbonylaminomethyl)-5,6,7,8-tetrahydronaphthalen-2-yl]methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In dichloromethane (5 ml), the (2RS)-2-(N-tert-

butoxycarbonylaminomethyl)-6-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (0.19 g) was dissolved. Pyridinium chlorochromate (0.17 g) was added to the resulting solution, followed by stirring at room temperature for 2 hours. The reaction mixture was purified as it was by chromatography on a silica gel column (hexane : ethyl acetate = 4:1), whereby a colorless solid (0.16 g) was obtained. The resulting solid was dissolved in dichloromethane (8 ml), followed by the addition of 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine trifluoroacetate (0.24 g), triethylamine (80.0 µl) and sodium triacetoxymethylborohydride (0.17 g). The resulting mixture was stirred at room temperature for 16 hours under an argon gas atmosphere. An aqueous solution of sodium bicarbonate was added to the reaction mixture. The resulting mixture was diluted with dichloromethane to separate the organic layer. The organic layer was dried over sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1), whereby a colorless viscous liquid (0.33 g, 86%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.30-1.50 (1H,m), 1.44 (9H,s), 1.80-2.00 (2H,m), 2.40 (1H,m), 2.51 (4H,br), 2.60-2.90 (3H,m), 3.09 (6H,br), 3.39 (2H,s), 4.67 (1H,br), 6.90-7.00 (3H,m), 7.56 (1H,d,J=8.8Hz), 7.77 (1H,d,J=8.8Hz), 7.80-8.00 (3H,m), 8.28 (1H,s).

MS (FAB)  $m/z$ : 584  $[(M+H)^+, Cl^{35}]$ , 586  $[(M+H)^+, Cl^{37}]$ .

[Referential Example 322] (2RS)-2-(tert-Butyldimethylsilyloxymethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene

5 In N,N-dimethylformamide (5 ml), (2RS)-2-hydroxymethyl-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene (1.71 g) was dissolved. To the resulting solution, imidazole (0.81 g) and tert-butyldimethylsilyl chloride (1.81 g) were added under ice  
10 cooling, followed by stirring at room temperature for 14 hours. After the addition of methanol, the mixture was concentrated under reduced pressure. The concentrate was diluted with ethyl acetate, washed with water and then dried over anhydrous sodium sulfate. The residue obtained  
15 by distilling off the solvent under reduced pressure was purified by chromatography (hexane : ethyl acetate = 50:1), whereby a pale yellow solid (2.20 g, 85%) was obtained.

$^1H$ -NMR ( $CDCl_3$ )  $\delta$ : 0.06(6H,s), 0.91(9H,s), 1.40-1.60(1H,m), 1.90-2.10(2H,m), 2.53(1H,dd,J=17.1,10.3Hz), 2.80-  
20 3.00(3H,m), 3.58(2H,d,J=5.9Hz), 3.89(3H,s), 7.14(1H,d,J=7.8Hz), 7.70-7.80(2H,m).

MS (FAB)  $m/z$ : 335  $(M+H)^+$ .

[Referential Example 323] (2RS)-2-(tert-Butyldimethylsilyloxymethyl)-6-hydroxymethyl-1,2,3,4-  
25 tetrahydronaphthalene

In the same manner as in Referential Example 320, the

title compound was obtained using (2RS)-2-(tert-butyltrimethylsilyloxymethyl)-6-methoxycarbonyl-1,2,3,4-tetrahydronaphthalene as a starting material.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.07(6H,s), 0.91(9H,s), 1.30-1.50(1H,m),  
5 1.50-1.60(1H,m), 1.90-2.10(2H,m), 2.48(1H,m), 2.70-  
2.90(3H,m), 3.58(2H,m), 4.62(2H,d,J=5.9Hz), 7.09(3H,m).

MS (FAB)  $m/z$ : 307 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 324] (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-2-(tert-butyltrimethylsilyloxymethyl)-1,2,3,4-tetrahydronaphthalene

In dichloromethane (10 ml), (2RS)-2-(tert-butyltrimethylsilyloxymethyl)-6-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (1.00 g) was dissolved.

Triethylamine (0.5 ml) was added to the resulting solution,  
15 followed by ice cooling. A solution of methanesulfonyl chloride (0.39 g) in dichloromethane (1 ml) was added to the reaction mixture and the mixture was stirred at room temperature for 9 hours. After washing with water, the reaction mixture was dried over anhydrous sodium sulfate.

20 The residue obtained by distilling off the solvent under reduced pressure was treated in the same manner as in Referential Example 318, whereby the title compound (1.10 g, 83%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.06(6H,s), 0.91(9H,s), 1.40-1.60(1H,m),  
25 1.46(9H,s), 1.90-2.00(2H,m), 2.45(1H,m), 2.70-2.90(3H,m),  
3.57(2H,m), 4.24(2H,m), 4.76(1H,br), 7.00-7.10(3H,m).

MS (FAB)  $m/z$ : 406 (M+H)<sup>+</sup>.

[Referential Example 325] (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene

5           In tetrahydrofuran (10 ml), (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-2-(tert-butyltrimethylsilyloxymethyl)-1,2,3,4-tetrahydronaphthalene (1.09 g) was dissolved. Tetrabutylammonium fluoride (a 1.0M tetrahydrofuran solution, 4.0 ml) was added to the  
10           resulting solution, followed by stirring at room temperature for 2 hours. After concentration under reduced pressure, the reaction mixture was diluted with dichloromethane, washed with water and dried over anhydrous sodium sulfate. The residue obtained by distilling off the  
15           solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 3:1 to 2:1), whereby a colorless solid (0.77 g, 98%) was obtained. A portion of the solid was recrystallized from a mixed solvent of hexane and ethyl  
20           acetate, whereby colorless crystals were obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.40-1.60 (2H, m), 1.46 (9H, s), 1.90-2.10 (2H, m), 2.48 (1H, dd,  $J=16.6, 10.7$  Hz), 2.70-3.00 (3H, m), 3.6-3.7 (2H, m), 4.24 (2H, d,  $J=5.4$  Hz), 4.78 (1H, br), 7.00-7.10 (3H, m).

25           Elementary analysis for C<sub>17</sub>H<sub>25</sub>NO<sub>3</sub>  
Calculated: C, 70.07; H, 8.65; N, 4.81.

Found: C, 70.02; H, 8.61; N, 4.46.

[Referential Example 326] 1-[[ (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

5 In dichloromethane (5 ml), (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (0.17 g) was dissolved, followed by the addition of N-methylmorpholine N-oxide (0.13 g) and molecular sieves 4A (activated powder, 0.18 g). Under ice  
10 cooling, tetrapropylammonium perruthenate (10 mg) was added and the mixture was stirred at room temperature for 1 hour. Diethyl ether was added to the reaction mixture. From the resulting mixture, insoluble matter was removed by filtration through Celite. The filtrate was distilled  
15 under reduced pressure. The residue was purified by chromatography on a silica gel column (dichloromethane) to yield the aldehyde compound. In the same manner as in Referential Example 321, a reaction was effected using the resulting aldehyde compound, whereby the title compound  
20 (0.14 g, 41%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.20-1.40 (1H, m), 1.44 (9H, s), 1.80-2.00 (2H, m), 2.20-2.40 (3H, m), 2.50-2.60 (4H, m), 2.60-2.80 (3H, m), 3.11 (4H, m), 4.20 (2H, d,  $J=5.4\text{Hz}$ ), 4.79 (1H, br), 6.94 (3H, m), 7.57 (1H, dd,  $J=8.8, 1.5\text{Hz}$ ),  
25 7.79 (1H, dd,  $J=8.8, 1.5\text{Hz}$ ), 7.90-8.00 (3H, m), 8.31 (1H, s).

MS (FAB)  $m/z$ : 584  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 586  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .



[Referential Example 327] 1-[[ (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

5           In carbon tetrachloride (2 ml), acetonitrile (2 ml) and water (3 ml), (2RS)-6-(N-tert-butoxycarbonylaminomethyl)-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalen (0.21 g) was dissolved. To the resulting solution, sodium periodate (0.48 g) and ruthenium  
10 trichloride hydrate (4 mg) were added, followed by stirring for 90 minutes. The reaction mixture was diluted with dichloromethane. The organic layer thus separated was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was  
15 added with diethyl ether. After the filtration of insoluble matter, the filtrate was distilled under reduced pressure. The carboxylic acid compound thus obtained was reacted in the same manner as in Referential Example 319, whereby the title compound (0.11 g, 25%) was obtained.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.45 (9H, s), 1.70-2.00 (2H, m), 2.60-2.90 (4H, m), 2.95 (1H, m), 3.11 (4H, m), 3.64 (2H, m), 3.76 (2H, m), 4.22 (2H, d, J=5.4 Hz), 4.82 (1H, br), 6.90-7.10 (3H, m), 7.59 (1H, d, J=8.8 Hz), 7.77 (1H, d, J=8.8 Hz), 7.90-8.00 (3H, m), 8.31 (1H, s).

25 MS (FD) m/z: 597 (M<sup>+</sup>, Cl<sup>35</sup>), 599 (M<sup>+</sup>, Cl<sup>37</sup>).

[Referential Example 328] 2-(N-tert-

Butoxycarbonylaminomethyl)-7-methoxycarbonylnaphthalene

In the same manner as in Referential Example 324, a reaction was effected using 2-hydroxymethyl-7-methoxycarbonylnaphthalene (1.01 g) as a starting material, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49(9H,s), 3.98(3H,s), 4.50(2H,d,J=5.4Hz), 4.99(1H,br), 7.53(1H,d,J=8.3Hz), 7.80-7.90(3H,m), 8.04(1H,dd,J=8.3,1.0Hz), 8.57(1H,s).

Elementary analysis for  $\text{C}_{18}\text{H}_{21}\text{NO}_4$

Calculated: C, 68.55; H, 6.71; N, 4.44.

Found: C, 68.54; H, 6.70; N, 4.46.

[Referential Example 329] 1-[[7-(N-tert-butoxycarbonylaminomethyl)naphthalen-2-yl]carbonyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 319, a reaction was effected using 2-(N-tert-butoxycarbonylaminomethyl)-7-methoxycarbonylnaphthalene as a starting material, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.46(9H,s), 3.12(4H,br), 3.50-4.00(4H,br), 4.45(2H,d,J=5.9Hz), 5.01(1H,br), 7.34(1H,d,J=7.8Hz), 7.45(1H,d,J=8.3Hz), 7.50-7.60(1H,m), 7.66(1H,s), 7.70-7.80(4H,m), 7.90-8.00(3H,m), 8.30(1H,s).  
MS (FAB)  $m/z$ : 594  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 596  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 330] 1-[[7-(N-tert-

Butoxycarbonylaminomethyl)naphthalen-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 320 or Referential Example 326, a reaction was effected using 2-(N-tert-butoxycarbonylaminomethyl)-7-methoxycarbonylnaphthalene as a starting material, whereby the title compound was obtained.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47 (9H, s), 2.50-2.70 (4H, m), 3.10 (4H, br), 3.61 (2H, s), 4.44 (2H, d, J=5.4 Hz), 4.92 (1H, br), 7.30-7.40 (2H, m), 7.50-7.70 (3H, m), 7.70-7.90 (3H, m), 7.90-8.00 (3H, m), 8.29 (1H, s).

MS (FAB) m/z: 580 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 582 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 331] 2-(N-tert-butoxycarbonylaminomethyl)-6-methoxycarbonylnaphthalene

In a mixed solvent of tetrahydrofuran (40 ml) and methanol (8 ml), dimethyl 2,6-naphthalenedicarboxylate (2.00 g) was suspended. To the resulting suspension, sodium borohydride (0.98 g) was added under ice cooling, followed by stirring at room temperature for 21 hours. The reaction mixture was added with water and then concentrated under reduced pressure. Ethyl acetate and dilute hydrochloric acid were added to the residue to separate the organic layer. The organic layer was dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl

acetate = 3:1), whereby colorless crystals (1.23 g, 70%) was obtained. The resulting crystals were reacted as in Referential Example 324, whereby the title compound was obtained.

5  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.48(9H,s), 3.98(3H,s),  
4.50(2H,d,J=5.4Hz), 4.99(1H,br), 7.47(1H,d,J=8.3Hz),  
7.75(1H,s), 7.84(1H,d,J=8.8Hz), 7.92(1H,d,J=8.8Hz),  
8.06(1H,d,J=8.3Hz), 8.58(1H,s).

Elementary analysis for  $\text{C}_{18}\text{H}_{21}\text{NO}_4$

10 Calculated: C, 68.55; H, 6.71; N, 4.44.

Found: C, 68.93; H, 6.70; N, 4.29.

[Referential Example 332] Methyl 5-benzimidazolecarboxylate hydrochloride

Under ice cooling, thionyl chloride (2.30 ml) was  
15 added dropwise to methanol (50 ml). Then, 5-benzimidazolecarboxylic acid (5.00 g) was added, followed by heating under reflux for 5 hours. The reaction mixture was distilled under reduced pressure. The residue was pulverized in diethyl ether, followed by collection through  
20 filtration, whereby colorless crystals (6.36 g, 97%) was obtained.

$^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ )  $\delta$ : 3.93(3H,s), 7.96(1H,d,J=8.8Hz),  
8.12(1H,d,J=8.8Hz), 8.40(1H,s), 9.66(1H,s).

Elementary analysis for  $\text{C}_9\text{H}_8\text{N}_2\text{O}_2 \cdot \text{HCl}$

25 Calculated: C, 50.84; H, 4.27; N, 13.17; Cl, 16.67.

Found: C, 50.64; H, 4.22; N, 13.12; Cl, 16.59.

[Referential Example 333] Methyl N-triphenylmethyl-5-benzimidazolecarboxylate

In dichloromethane (15 ml), methyl 5-benzimidazolecarboxylate hydrochloride (1.00 g) was suspended. To the resulting suspension, triethylamine (1.50 ml) and triphenylmethyl chloride (1.50 g) were added, followed by stirring at room temperature for 3 hours. The reaction mixture was diluted with dichloromethane, washed with water, and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel column (hexane : ethyl acetate = 2:1), whereby title compound (2.10 g, quant.) was obtained as a yellow solid.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.75(2H,s), 3.89(1H,s), 6.49(1/3H,d,J=8.8Hz), 7.1-7.4(16H,m), 7.61(1/3H,dd,J=8.8,1.5Hz), 7.78(2/3H,d,J=8.8Hz), 7.87(2/3H,dd,J=8.8,1.5Hz), 7.96(1/3H,s), 8.02(2/3H,s).

MS (FAB)  $m/z$ : 419 ( $\text{M}+\text{H}$ ) $^+$ .

[Referential Example 334] Sodium thiazolo[5,4-c]pyridine-2-carboxylate

Ethyl thiazolo[5,4-c]pyridine-2-carboxylate (J. Heterocyclic Chem., **27**, 563(1990) (0.61 g) was dissolved in tetrahydrofuran (12 ml). To the resulting solution, a 1N aqueous sodium hydroxide solution (3 ml) was added, followed by stirring at room temperature for 30 minutes.

The insoluble matter was collected by filtration. Without purification, it was provided for the subsequent reaction as it was.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 7.95(1H,d,J=5.9Hz), 8.57(1H,d,J=5.9Hz),  
 5 9.27(1H,s).

[Referential Example 335] 1-[(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)methyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

10 In the same manner as in Referential Example 321, the title compound was obtained using 5-tert-butoxycarbonyl-2-formyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (WO94/21599) and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.47(9H,s), 2.53-2.62(4H,m), 2.72(2H,br  
 15 s), 3.10(4H,br s), 3.59(2H,s), 3.66(2H,br s), 4.38(2H,s), 6.54(1H,s), 7.57(1H,dd,J=8.8,2.0Hz), 7.76(1H,dd,J=8.8,2.0Hz), 7.87-7.94(3H,m), 8.29(1H,s).

MS (FAB) m/z: 562 [(M+H)<sup>+</sup>, Cl<sup>35</sup>], 564 [(M+H)<sup>+</sup>, Cl<sup>37</sup>].

[Referential Example 336] 3-(5-tert-Butoxycarbonyl-4,5,6,7-terahydrothieno[3,2-c]pyridin-2-yl)propionic acid  
 20

Under ice cooling, sodium hydride (about 60% in oil, 126 mg) was added to tetrahydrofuran (10 ml). After stirring for 5 minutes, ethyl diethylphosphonoacetate (0.42 ml) was added dropwise and the resulting mixture was  
 25 stirred for 30 minutes under ice cooling. To the reaction mixture, a solution of 5-tert-butoxycarbonyl-2-formyl-

4,5,6,7-tetrahydrothieno[3,2-c]pyridine (W094/21599) (360 mg) in tetrahydrofuran (10 ml) was added dropwise, followed by stirring for 1 hour under ice cooling. The reaction mixture was then concentrated under reduced pressure.

5 Ethyl acetate was added to the concentrate. The mixture was washed with water and saturated aqueous NaCl solution and dried over anhydrous sodium sulfate. The residue obtained by distilling off the solvent under reduced pressure was purified by chromatography on a silica gel  
10 column (hexane : ethyl acetate = 5:1), whereby a yellow oil (515 mg, quant) was obtained.

The resulting oil (1.38 g, 4.09 mmol) was dissolved in methanol (40 ml), followed by the addition of 10% palladium carbon (0.20 g). The mixture was subjected to catalytic  
15 reduction for 1 hour under normal pressure. After the removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure, whereby pale yellow oil (1.41 g, quant.) was obtained.

The oil (1.38 g, 4.07 mmol) was dissolved in  
20 tetrahydrofuran (15 ml), followed by the addition of ethanol (10 ml) and a 1N aqueous sodium hydroxide solution (8 ml). The resulting mixture was heated under reflux for 30 minutes. To the reaction mixture, 1N hydrochloric acid and ethyl acetate were added to separate the organic layer.  
25 The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent,

whereby the title compound (1.28 g, quant.) was obtained as a colorless oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48 (9H, s), 2.70 (2H, t,  $J=7.3\text{Hz}$ ),  
2.76 (2H, br s), 3.09 (2H, t,  $J=7.3\text{Hz}$ ), 3.70 (2H, s), 4.40 (2H, s),  
5 6.51 (1H, s).

MS (FD)  $m/z$ : 311 $\text{M}^+$ .

[Referential Example 337] (E)-3-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)acrylic acid

In the same manner as in Referential Example 336  
10 except that hydrolysis was carried out instead of catalytic hydrogenation, whereby the title compound was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.49 (9H, s), 2.85 (2H, br s), 3.73 (2H, br s),  
4.47 (2H, s), 6.12 (1H, d,  $J=15.4\text{Hz}$ ), 6.98 (1H, s),  
7.77 (1H, d,  $J=15.4\text{Hz}$ ).

15 MS (FD)  $m/z$ : 309 $\text{M}^+$ .

[Referential Example 338] 1-(E)-3-(5-tert-Butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propenoyl]-4-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In the same manner as in Referential Example 319, a  
20 reaction was effected using (E)-3-(5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)acrylic acid and 1-[(6-chloronaphthalen-2-yl)sulfonyl]piperazine hydrochloride as starting materials, whereby the title compound was obtained.

25  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47 (9H, s), 2.80 (2H, br s),



3.12 (4H, t, J=4.9 Hz), 3.46-3.86 (6H, m), 4.41 (2H, s),  
6.39 (1H, d, J=15.1 Hz), 6.83 (1H, s), 7.55-7.78 (3H, m), 7.89-  
7.92 (3H, m), 8.30 (1H, s).

MS (FD) m/z: 601 ( $M^+$ ,  $Cl^{35}$ ), 603 ( $M^+$ ,  $Cl^{37}$ ).

5 [Referential Example 339] 1-[3-(5-tert-butoxycarbonyl-  
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionyl]-4-  
[(6-chloronaphthalen-2-yl)sulfonyl]piperazine

In tetrahydrofuran (10 ml), 3-(5-tert-butoxycarbonyl-  
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propionic acid  
10 (445 mg) was dissolved, followed by the successive dropwise  
addition of N-methylmorpholine (170  $\mu$ l) and isobutyl  
chloroformate (210  $\mu$ l) at  $-20^{\circ}\text{C}$ . After stirring at  $-20^{\circ}\text{C}$   
for 10 minutes, a solution of 1-[(6-chloronaphthalen-2-  
yl)sulfonyl]piperazine hydrochloride (607 mg) which had  
15 been dissolved in dichloromethane (10 ml) was added. After  
stirring at  $-20^{\circ}\text{C}$  for 10 minutes, the reaction mixture was  
warmed up to room temperature. The reaction mixture was  
concentrated under reduced pressure. The residue was then  
dissolved in dichloroethane. The resulting solution was  
20 washed with 1N hydrochloric acid, a saturated aqueous  
solution of sodium bicarbonate and saturated aqueous NaCl  
solution, dried over anhydrous sodium sulfate and then  
distilled under reduced pressure to remove the solvent.  
The residue was purified by chromatography on a silica gel  
25 column (hexane : ethyl acetate = 4:1 to 2:1), whereby the  
title compound (625 mg, 72%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.47 (9H, s), 2.53 (2H, t,  $J=7.5\text{Hz}$ ),  
2.68 (2H, br s), 2.99-3.10 (6H, m), 3.51-3.55 (2H, m), 3.64 (2H, br  
s), 3.72-3.77 (2H, m), 4.34 (2H, s), 6.43 (1H, s),  
7.59 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.74 (1H, dd,  $J=8.8, 2.0\text{Hz}$ ), 7.88-  
5 7.94 (3H, m), 8.30 (1H, s).

MS (FAB)  $m/z$ : 604  $[(\text{M}+\text{H})^+, \text{Cl}^{35}]$ , 606  $[(\text{M}+\text{H})^+, \text{Cl}^{37}]$ .

[Referential Example 340] 3-(5-tert-Butoxycarbonyl-  
4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)propanal

In dichloromethane (100 ml), ethyl 3-(5-tert-  
10 butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-  
yl)propionate (1.68 g) obtained in Referential Example 336  
was dissolved. After stirring at  $-78^\circ\text{C}$  for 10 minutes,  
diisobutylaluminum hydride (a 0.98M hexane solution, 7.50  
ml) was slowly added dropwise. After stirring at  $-78^\circ\text{C}$  for  
15 10 minutes, methanol (50 ml) was added, followed by warming  
up to room temperature. The reaction mixture was  
concentrated under reduced pressure. To the residue,  
dichloromethane and a saturated aqueous solution of  
ammonium chloride were added, followed by Celite  
20 filtration. The organic layer was separated from the  
filtrate, washed with saturated aqueous NaCl solution,  
dried over anhydrous sodium sulfate and distilled to remove  
the solvent. The residue was purified by chromatography on  
a silica gel column (hexane : ethyl acetate = 5:1), whereby  
25 the title compound (935 mg, 55%) was obtained.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.48 (9H, s), 2.76 (2H, br s),